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CONTENTS FOR JULY, 1930

Food Allergens. I. A Genetic Classification, With Results of Group Testing. By Warren T. Vaughan, M.D., Richmond, Virginia. 385

The Significance of Local Reaction in the Skin Following Deep and Superficial Injections of Pollen Extracts. By Leslie N. Gay, M.D., Baltimore, Md. 403

Ragweed Hay Fever. Its Diagnosis and Treatment. By Harry Markow, M.D., and W. C. Spain, M.D., New York City 414

Studies of Bronchial Secretion. By W. B. Kountz, M.D., and Karl Koenig, B.S., St. Louis, Mo. 429

Sudden Death From Bronchial Asthma. By John A. Murphy, M.D., and E. A. Case, M.D., Philadelphia, Pa. 434

Skin Tests in Normal Individuals With Mixtures of Atopen and Reagin. By Louis B. Baldwin, M.D., Rochester, N. Y. 438

Sensitivity Due to Christmas Trees: A Seasonal Stopen in Bronchial Asthma. By Herbert Marshall Cobe, M.D., Philadelphia, Pa. 442

Some Findings of Antral Studies With Iodized Oil in Patients With Bronchial Asthma. By Philip S. Stout, M.D., Philadelphia, Pa. 446

Society Proceedings 455

The Society for the Study of Asthma and Allied Conditions. Sixth Annual Meeting, Atlantic City, May 3, 1930 455

Ragweed Dermatitis. By Otelia Bengtsson, M.D., Ossinging, New York 457

Quantitative Skin Tests With Bacterins Prepared From the B. Coli Group. By L. W. Famulener, M.D., and John Staige Davis, Jr., M.D., New York 457

Active Immunization Against Typhoid Fever With Particular Reference to an Intradermal Method. By Louis Tuft, M.D., Philadelphia 462

A Test Tube Neutralization Method for Studying the Identity and Properties of Reagins. By Matthew Walzer, M.D., and Katherine Bowman, New York City 464

Deformity of the Face Caused by Nasal Allergy in Childhood. By W. W. Duke, M.D., Kansas City 466

Chemical and Clinical Studies on Pollen (Preliminary Report). By Arthur Stull, M.D., Robert Chobot, M.D., and Robert A. Cooke, M.D., New York City 470

Observations on Certain Castor Bean Extracts. By James H. Barnard, M.D., New York City 473

Linseed Meal Sensitization. By Grafton Tyler Brown, M.D., Washington, D. C. 475

Selected Abstracts 476

The Journal of Allergy

VOL. I JULY, 1930 NO. 5

Original Articles

FOOD ALLERGENS

I. A GENETIC CLASSIFICATION, WITH RESULTS OF GROUP TESTING*

WARREN T. VAUGHAN, M.D.
RICHMOND, VIRGINIA

THOSE whose study of allergy has carried them into the field of pollen sensitization have adopted the botanical nomenclature and classification of pollens and pollen-producing plants. The first great advantage of this is one of standardization, since popular names of plants are often applied to different varieties in different sections of the country. A second advantage is that biologic relationship being recognized, we have been able to demonstrate allergic crossed relationships.

To a limited degree this crossed relationship has also been known to exist among animal allergens. This has been shown, for example, among the feathers, and it has been stated† that the epidermal proteins of cloven-hoofed animals are likely to show crossed reactions.

The present study was undertaken for several reasons. First, I feel that the classification of food allergens should be placed on a biologic basis. Second, I have gained the impression from previous observation that if the grouping of foods were properly systematized, we would find evidence of crossed or group allergic reactions. Third, I conceived it as possible that a proper grouping of chemically, closely related allergens in a single intradermal test might give positive reaction when the individual members were apparently negative, as a result of very mild cutaneous reactivity. If this should turn out to be the case, the procedure of grouping would materially increase our diagnostic efficiency. Finally, it seems possible that an individual shown by skin test to be sensitive to one member of a biologic group might be sensitive to another closely related member, even though the customary reaction was negative.

In the present discussion we shall consider only the vegetable foods.

*Read at the Sixth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, May 3, 1930.

†Balyeat, personal communication.

TABLE I

BOTANICAL CLASSIFICATION OF EDIBLE PLANTS

FAMILY	GENUS	SPECIES	COMMON NAME
		Monocotyledones	
Graminae	Triticum	sativum	Wheat
	Secale	cereale	Rye
	Hordeum	vulgare	Barley
	Avena	sativa	Oat
	Oryza	sativa	Rice
	Zea	mays	Corn
Palmaceae	Cocos	nucifera	Cocoanut
	Phoenix	dactylifera	Date
Bromeliaceae	Ananus	sativus	Pineapple
Liliaceae	Allium	cepa	Onion
		sativum	English garlic
	Asparagus	officinalis	Asparagus
Musaceae	Musa	sapientum	Banana
Zinziberaceae	Zinziber	officinale	Ginger
		Dicotyledones	
Moraceae	Morus	nigra	Black mulberry
	Ficus	carica	Fig
Polygonaceae	Fagopyrum	vulgare	Buckwheat
	Pheum	rhaponticum	Rhubarb
Juglandaceae	Juglans	nigra	Black walnut
		regia	English walnut
	Carya	olivaeformis	Pecan
		alba	Hickory
Betulaceae	Corylus	avellana	Hazelnut, filbert
	Castanea	dentata	Chestnut
Chenopodiaceae	Spinacia	oleracea	Spinach
	Beta	vulgaris	Beet
		cycla	Swiss chard
Grossulariaceae	Ribes	vulgare	Currant
		oeyacanthoides	Gooseberry
Cruciferae	Raphanus	sativus	Radish
	Radicula	armoracia	Horseradish
		nasturtium aquatium	Water cress
	Brassica	rapa	Turnip
		campestris	Rutabaga
		alba	White mustard
		nigra	Brown mustard
		oleracea capitata	Cabbage
		oleracea acephala	Kale
		oleracea gemmifera	Brussels sprouts
		oleracea caulo-rapa	Kohlrabi
		oleracea botrytis	Cauliflower (Broccoli)
Rosaceae	Rubus	nigrobaccus	Blackberry
		occidentalis	Black raspberry
		strigosus	Red raspberry
	Fragaria	chiloensis	Strawberry
Pomaceae	Malus	sylvestris	Apple
	Pyrus	communis	Pear
Drupaceae	Prunus	amygdalus	Almond
		domestica	Plum, prune
		avium	Cherry
		armeniaca	Apricot
		persica	Peach
Leguminosae	Pisum	sativum	Pea
	Phaseolus	vulgaris	Kidney bean
		lunatus	Lima bean
	Lens	esculenta	Lentil
	Acharis	hypogaea	Peanut

TABLE I.—CONT'D

FAMILY	GENUS	SPECIES	COMMON NAME
		Dicotyledones	
Rutaceae	Citrus	limonia	Lemon
		grandis	Grapefruit
		sinensis	Common orange
Anacardiaceae	Pistacia	vera	Pistachio nut
Vitaceae	Vitis	vinifera	Grape, raisin
Malvaceae	Gossypium	hirsutum barbadense	Cotton seed
	Hibiscus	esculentus	Okra, gumbo
Sterculiaceae	Theobroma	cacao	Cocoa
Theaceae	Thea	sinensis	Tea
Umbelliferae	Daucus	carota	Carrot
	Pastinaca	sativa	Parsnip
	Apium	petroselinum	Parsley
		graveolens	Celery
Vacciniaceae	Gaylussacia	resinosa	Huckleberry
	Vaccinium	macrocarpon	Cranberry
Oleaceae	Olea	europoea	Olive
Convolvulaceae	Ipomoea	batatas	Sweet potato
Solanaceae	Solanum	tuberosum	Potato
		melongena	Eggplant
	Lycopersicum	esculentum	Tomato
Rubiaceae	Coffea	arabica	Coffee
Cucurbitaceae	Cucurbita	pepo	Pumpkin
		moschata	Winter squash
		maxima	Hubbard squash
	Cucumis	melo	Cantaloupe
		sativus	Cucumber
	Citrullus	vulgaris	Watermelon
Compositae (Chichoriaceae)	Lactuca	sativa	Lettuce
	Tragopogon	porrifolius	Salsify, oyster plant
	Chicorium	intybus	Chicory
		endiva	Endive
Compositae (Asteraceae)	Helianthus	tuberosus	Jerusalem artichoke
	Cynara	scolymus	Artichoke

The customary classification of foods as allergens appears to be either alphabetical or purely culinary, and includes such groups as nuts, fruits, berries, legumes, leafy vegetables, starchy vegetables, etc.

The classification herein presented was developed through the cooperation of Doctor Frances H. Wilson, professor of botany in the University of Richmond, and the food extracts were furnished by H. K. Mulford Company, who contributed the facilities of their laboratories. I wish to express special appreciation to Doctor C. Roos of the Mulford laboratories for his cooperation in preparing the food extracts employed.

The ideal biologic classification from the viewpoint of allergy would naturally be a chemical one; but, since none was available, it became necessary to choose a botanical grouping. Theoretically, this probably fairly closely approximates the chemical classification, since the grouping of plants is based not on gross morphology but upon the structural and functional characteristics of the reproductive organs. We may presume that the proteins of the reproductive organs are less subject to environmental and developmental change than those of other por-

tions of the plant. The constitution of the specific protein is probably more dependent upon the characteristics of the reproductive organs than on the more highly differentiated special tissues which cannot alone reproduce themselves.

The classification shown in Table I is that used in the present study and follows the accepted botanical distribution, beginning with the simpler plants, the monocotyledones and progressing through the dicotyledones. In it we discover somewhat surprising relationships. We observe that the peanut is a member of the leguminosae and is much more closely related to peas and beans than it is to almond, which is a member of the drupaceae, and a cousin of cherry, apricot, and peach. Indeed, the chief epicurean difference between almond and peach is that, of the latter one eats the outside and of the former the inside.

Potato according to this grouping is more closely related to tomato than it is to sweet potato. Those who have lived on the farm recall, no doubt, that the fruit of the potato plant is a small organ scarcely larger than the tip of the finger which resembles very much a miniature tomato. The sweet potato belongs to quite a different group, the convolvulaceae, the morning-glory family. With the potato and tomato, as with many others to be discussed, the culinary and morphologic difference depends chiefly upon which portion of the plant undergoes greatest development. In the potato it is the stem or a modified stem (the tuber), while in the tomato it is the fruit. The sweet potato, on the other hand, is a root.

The only relationship between buckwheat and wheat is in the spelling of the name.

The differentiation of organs is shown especially in the family cruciferae, in which the radish and turnip are roots, the edible portion of Brussels sprouts is a bud, kohl-rabi is a stem, cauliflower and broccoli are abortive flowers, cabbage represents the leaf, and mustard, the seed.

Among the chenopodiaceae, spinach represents a plant whose chief edible portion is the leaf. The beet is a tap root, and chard is the hyperplastic leaf of practically the same plant.

Among the liliaceae, onion and garlic are fleshy stems with overlapping fleshy leaves. Asparagus and chives are also leaves.

We might carry this classification even farther and say that among the alimentary and inhalant allergens, the cereal grains are more closely related to the pollens of the grasses than to other foods; onion, garlic, and asparagus are more closely related to the lily, hyacinth, and tulip; swiss chard, beet, and spinach to the chenopodiaceae, such as lamb's quarters (chenopodium album); strawberry, blackberry, and raspberry to the rose and spirea; the pea-bean family to clover and alfalfa; grape to American ivy and the Virginia creeper; cotton seed and okra to hibiscus, hollyhock, and marshmallow; lettuce, chicory, and endive to

dandelion; and artichoke to ragweed and thistle. If our hypotheses be correct, one might anticipate finding crossed reactions to some of these pollens when one finds sensitization in that food group. For the present we will state that so far we have found only a few instances of sensitization to wind-borne pollens of the same family.

In preparing the protein extracts the solutions were arranged as in Table II. In general, botanical families were grouped together into one solution. In the case of grape and okra and of banana and ginger there is no botanical association, these groupings being made merely to diminish the number of needlings necessary. In the case of the cereal grains (although with the exception of corn there is a fairly close relationship) only individual tests were made, for, when the patient was found wheat sensitive, it was necessary to know the reaction to the other individual cereals in order to prescribe substitute flours.

TABLE II

FOOD PROTEIN GROUPS*

1. Walnut	Kidney bean	Cantaloupe
Pecan	Lentil	Cucumber
2. Swiss Chard	Peanut	Watermelon
Beet	String bean	14. Lettuce
Spinach	7. Lemon	Artichoke
3. Radish	Orange	15. Rye
Turnip	Grapefruit	16. Wheat
Cabbage	8. Grape	17. Barley
Cauliflower	Okra	18. Oat
Mustard	9. Cocoa	19. Rice
4. Blackberry	10. Parsley	20. Corn
Strawberry	Celery	21. Onion
Raspberry	Parsnip	Garlic
5. Almond	Carrot	Asparagus
Cherry	11. Sweet potato	22. Banana
Apricot	12. Tomato	Ginger
Plum	Potato, Irish	29. Apple
Peach	Eggplant	Pear
6. Pea	13. Pumpkin	
Lima bean	Squash	

*Test solutions 23-28 represent animal foods.

Testing was done both with the groups as indicated and with the individual foods. The concentration of the individual extracts was 500 units per c.c. This, in accordance with the Mulford system of extraction represents 0.08 milligram of nitrogen per c.c. In the group extracts the concentration was such as to represent 0.08 mg. nitrogen from each of the ingredients in each c.c. Therefore, in a mixture of three foods, there was three times as much allergen as in each of the three individual extracts. It is possible, although not demonstrated, that this higher content influenced nonspecifically the intensity of the reaction. Further comparative studies are being made with this in mind.

The results of this study do not lend themselves well to statistical interpretation. Thus, one would wish to know whether the increased concentration of allergenic material in some groups might cause non-

specifically a more intense dermal reaction. Table III shows the actual number of positive reactions observed in a series of 50 cases and the quantity of allergen as expressed in terms of nitrogen content, in each solution. In Fig. 1 this information is recorded graphically, showing the total number of prompt, positive reactions (column 5 in Table III) as compared with the protein unit concentration.

TABLE III

TEST EXTRACTS	PROMPT REACTIONS	DELAYED REACTIONS	PROMPT AND DELAYED	TOTAL PROMPT	UNITS (MULFORD)
1. Juglandaceae	3	0	0	3	1000
2. Chenopodiaceae	1	5	5	6	1500
3. Cruciferae	16	2	3	19	2500
4. Rosaceae	3	1	0	3	1500
5. Drupaceae	18	2	5	23	2500
6. Leguminosae	31	7	8	39	3000
7. Rutaceae	23	0	0	23	1500
8. Grape, okra	8	4	1	9	1000
9. Cocoa	7	2	1	8	500
10. Umbelliferae	25	4	5	30	2000
11. Sweet potato	2	0	0	2	500
12. Solanaceae	21	1	3	24	1500
13. Cucurbitaceae	5	7	11	16	2500
14. Compositae	10	6	4	14	1000
15. Rye	15	2	1	16	500
16. Wheat	1	4	0	1	500
17. Barley	5	2	0	5	500
18. Oat	3	1	0	3	500
19. Rice	12	1	1	13	500
20. Corn	8	3	3	11	500
21. Liliaceae	9	1	4	13	1500
22. Banana, ginger	15	5	6	21	1000
23. Beef, veal	5	1	0	5	1000
24. Milk	9	4	3	12	500
25. Egg	8	1	2	10	500
26. Chicken	1	1	0	1	500
27. Pork	0	0	0	0	500
28. Lamb	3	0	0	3	500
29. Pomaceae	1	10	3	4	500

The graph (Fig. 1) would indicate that although there are distinct variations, the higher the protein concentration the greater the likelihood of positive reactions, thus suggesting a nonspecific effect. On the other hand, one might argue equally well that nonspecific reaction does not play a part, since, for example, three groups containing 1,000 units gave a higher percentage of positives than two groups containing 1,500 units; or, again, two groups containing 1,500 units* give a higher proportion of positives than two other groups with 2,500 units.

A second argument against nonspecific effect might be that those food groups with higher frequency of positive reaction are known to be frequently allergenic irrespective of nitrogen content. A final argument against nonspecificity is that even though the percentage of positives is high, as, for example, in the legume group, it is not 100 per cent. There were some which gave negative reactions. Twenty-two per cent of the

*Line 7, Table III, through error is not represented in Fig. 7.

legume group gave negative prompt reactions, forty per cent of the carrot family (umbelliferae) were negative, and fifty-two per cent of the solanaceae.

We cannot at this time state definitely whether a nonspecific action is playing a part. We are carrying along further studies at the present time with this in view, first by testing with groups diluted to a constant concentration of 500 units per c.c. irrespective of the number of constituent allergens, and second, with control solutions containing 2,500 and 3,000 units in which the constituent allergens are not botanically related and are rarely positive reactors.

One might argue that it would be easy to tell whether a reaction was specific or nonspecific by observing whether the patient evidences symptoms after exposure to the positively reacting allergen. Unfortunately,

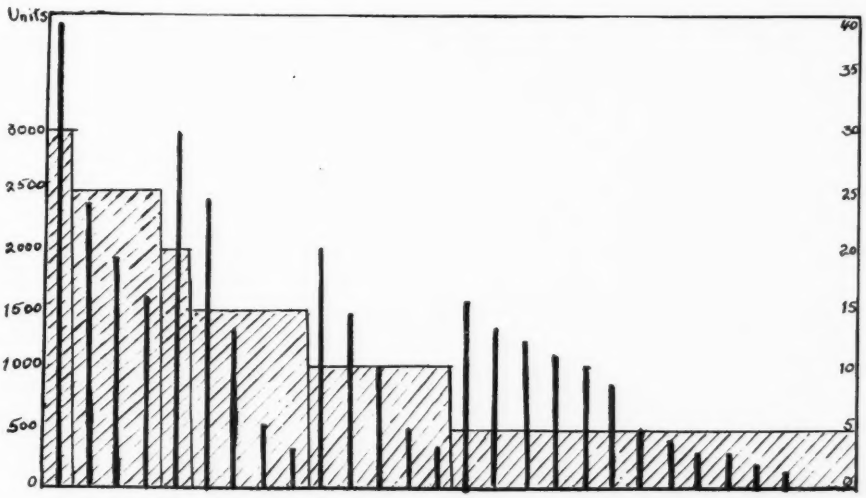


Fig. 1.

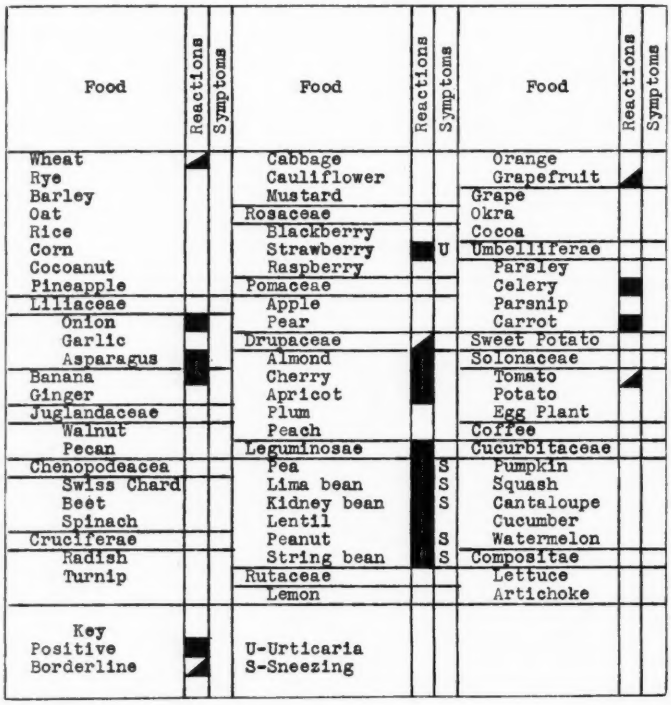
however, present opinion is that one may be sensitive by skin test to an allergen and yet not show symptoms on contact, except perhaps under certain circumstances. This is a matter of experience even when we are dealing with single test substances.

Another drawback to attempts at statistical study lies in the fact that every allergic person is an individual problem, the sensitization of one being, without obvious reason, to an altogether different allergen from that of another. As a consequence, the most interesting and instructive results of this study will be found in the protocols of the individual cases.

CASE REPORTS

CASE 1.—Diagnosis, vasomotor rhinitis, angioneurotic edema. This patient gave very strongly positive reactions to kidney bean, lima bean, peanut, string bean, lentil, and green pea, and a more strongly positive

reaction to the group leguminosae. Among the drupaceae he gave only a borderline reaction to the group, but a clear positive to cherry, apricot, and almond. Among the liliaceae the reaction was positive to onion and asparagus. He was not tested with the group allergens (liliaceae). Among the umbelliferae he reacted positively to celery and carrot. The group mixture was not tested. The only member of the solanaceae to which he reacted was the peppers. No group test was done. All the individual tests were made, as indicated in Table II, but only the two group tests indicated above were performed. The only two additional reactions were to strawberry and banana.



Case 1.

While a definite grouping is in evidence in this case, I wish particularly to call attention to the positive reactions to almond and peanut. Almond reacted in common with other members of the drupaceae, and peanut with other members of the leguminosae. Walnut and pecan, members of the family juglandeae, were negative. One might argue that the two positively reacting nuts might as logically be allergenically related to each other as to the other foods mentioned. The two following cases answer this objection.

Case 2.—This man has occasional attacks of acute enterocolitis traced to the eating of peaches. Until the autumn of 1929 no other foods had

produced reaction. He then found that nuts were producing similar symptoms. After repeated trial, however, he discovered that it was only a certain nut that caused trouble. He could eat peanuts, pecans, and walnuts without discomfort, almond alone producing colonic symptoms. This patient was not cognizant of my classification at the time, but it is noteworthy that almond and peach, the only offenders in his case, both belong among the drupaceae.

CASE 3.—This woman's complaint was indigestion, mucous colitis, and urticaria. She had learned from experience that cherry, prune, plum, apricot, and peaches produced attacks of colitis, urticaria, angioneurotic edema, swelling of the gums with bleeding of the mucous mem-

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Liliaceae			Apple		I	Parsnip		
Onion		I	Pear		I	Carrot		
Garlic			Drupaceae			Sweet Potato		
Asparagus			Almond			Solonaceae		
Banana			Cherry		IU	Tomato		
Ginger			Apricot		IU	Potato		
Juglandaceae			Plum		IU	Egg Plant		
Walnut			Peach		IU	Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea			Pumpkin		
Swiss Chard			Lima bean			Squash		
Beet			Kidney bean			Cantaloupe		
Spinach			Lentil			Cucumber		
Cruciferae			Peanut			Watermelon		
Radish			String bean			Compositae		
Turnip			Rutaceae			Lettuce		
			Lemon			Artichoke		

Case 3.

brane of the mouth, and itching in the mouth. Almond, so far as she knew, caused no trouble. On testing, however, she was found to be sensitive to cherry, apricot, and peach out of the four which she knew caused trouble, and almond gave a positive reaction both by dermal and intradermal tests. Peanut, walnut, and pecan were all negative, both by scratch and intradermally.

She knew that apples caused indigestion, and was found sensitive to apple both by scratch and intradermally. She was negative to pear by both tests, but stated that uncooked pear makes her mouth itch and swell. She tolerates canned pear without difficulty.

She gave borderline delayed reactions to the allergens of onion and asparagus, and had had attacks of vomiting after the eating of onion.

The other foods to which she gave positive reactions have not, so far as she knows, been productive of symptoms.

CASE 4.—Patient reacted positively to the group leguminosae but gave negative reactions to its constituent members. In view of this observation she made a study of subsequent manifestations, and found that green pea, lima and kidney bean, peanut, and string bean all produce urticaria. Peanut again falls in this group. She did not react to almond or to any member of that group or to the group mixture.

The findings in this case would also suggest that testing with the biologic group will demonstrate a sensitization that would have been

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat	◢		Cabbage	■		Orange		
Rye	◢		Cauliflower	◢		Grapefruit		
Barley	◢		Mustard			Grape		
Oat			Rosaceae			Okra	◢	
Rice	■	U	Blackberry			Cocoa	◢	
Corn			Strawberry			Umbelliferae	■	
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery	◢	U
Liliaceae			Apple			Parsnip	◢	U
Onion			Pear			Carrot		
Garlic			Drupaceae			Sweet Potato	◢	
Asparagus			Almond			Solonaceae		
Banana	◢		Cherry			Tomato		
Ginger			Apricot			Potato		
Juglandaceae			Plum			Egg Plant		
Walnut		I	Peach			Coffee		
Pecan			Leguminosae	■		Cucurbitaceae		
Chenopodeaceae			Pea		U	Pumpkin		
Swiss Chard			Lima bean		U	Squash	◢	
Beet			Kidney bean		U	Cantaloupe	■	
Spinach	◢		Lentil			Cucumber	■	
Cruciferae			Peanut		U	Watermelon		
Radish			String bean		U	Compositae		
Turnip			Rutaceae	◢		Lettuce	◢	
			Lemon			Artichoke		

Case 4.

overlooked by simply testing with the individual members. In this case the same observation also shows up in the family umbelliferae. Unfortunately, this is far from consistently the case. However, a few more similar examples will be of interest.

CASE 5.—Patient reacted positively to the groups cruciferae, leguminosae, umbelliferae, cucurbitaceae, but among the individual members the only positive reaction was to parsnip, with a borderline reaction to carrot. However, following subsequent study of her symptoms, she discovered that cabbage, peanut, carrot, and cucumber produced digestive disturbances, while the eating of celery caused eczema.

CASE 6.—This patient reacted to the group cucurbitaceae, but none of the individual reactions in this group was positive. She discovered,

Food	Reactions	Symptoms
Wheat	◢	E
Rye	◢	
Barley		
Oat	◢	
Rice	■	
Corn		
Cocoanut		
Pineapple		
Liliaceae		
Onion		I
Garlic		
Asparagus		
Banana		
Ginger		
Juglandaceae		
Walnut		
Pecan		
Chenopodeaceae	■	
Swiss Chard		
Beet		
Spinach		
Cruciferae	■	
Radish		
Turnip		
Cabbage		I
Cauliflower		
Mustard		
Rosaceae		
Blackberry		
Strawberry		
Raspberry		
Pomaceae		
Apple		
Pear		
Drupaceae		
Almond		
Cherry		
Apricot		
Plum		
Peach		
Leguminosae	■	
Pea		
Lima bean		
Kidney bean		
Lentil		
Peanut		I
String bean		
Rutaceae		
Lemon		
Orange		
Grapefruit		
Grape		
Okra		
Cocoa		
Umbelliferae	■	
Parsley		
Celery		E
Parsnip	■	
Carrot	◢	I
Sweet Potato		
Solonaceae	◢	
Tomato		
Potato		
Egg Plant		
Coffee	◢	
Cucurbitaceae	■	
Pumpkin		
Squash		
Cantaloupe		
Cucumber		I
Watermelon		
Compositae		
Lettuce		
Artichoke		

Case 5.

Food	Reactions	Symptoms
Wheat	◢	E
Rye	◢	
Barley	◢	
Oat	◢	
Rice	◢	
Corn	◢	
Cocoanut		
Pineapple		
Liliaceae	■	
Onion		
Garlic		I
Asparagus	◢	
Banana		
Ginger		
Juglandaceae		
Walnut		
Pecan		
Chenopodeaceae	◢	
Swiss Chard		
Beet		
Spinach		
Cruciferae	■	
Radish		
Turnip		
Cabbage		
Cauliflower		
Mustard		
Rosaceae		
Blackberry		
Strawberry		
Raspberry		
Pomaceae		
Apple		
Pear		
Drupaceae		
Almond		
Cherry		
Apricot		
Plum		
Peach		
Leguminosae	■	
Pea		
Lima bean	◢	
Kidney bean		
Lentil		
Peanut	◢	
String bean		
Rutaceae		
Lemon		I
Orange		
Grapefruit		
Grape		
Okra	◢	
Cocoa	◢	
Umbelliferae	■	
Parsley	◢	
Celery		
Parsnip		
Carrot		
Sweet Potato		
Solonaceae		
Tomato		
Potato		
Egg Plant		
Coffee		
Cucurbitaceae	■	
Pumpkin		
Squash		
Cantaloupe		I
Cucumber		I
Watermelon		
Compositae	■	
Lettuce		
Artichoke		

Case 6.

however, that cantaloupe and cucumber produced indigestion. The reaction to the liliaceae was positive, and she gave a borderline reaction to asparagus. Onion and asparagus were apparently without effect on trial, but garlic produced indigestion.

CASE 7.—This patient reacted to the groups drupaceae, rutaceae, and convolvulaceae, and while she did give a few positive individual reactions, her symptoms of vasomotor rhinitis were, with the exception of sweet potato, due to foods to which she gave negative individual reactions.

CASE 8 is of interest as showing crossed reactions in the family cruciferae. This man gave positive reactions to turnip and cabbage, and

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat			Cabbage			Orange		S
Rye			Cauliflower			Grapefruit		
Barley	◢		Mustard			Grape		
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa		
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Liliaceae			Apple			Parsnip		
Onion			Pear			Carrot		
Garlic			Drupaceae	■		Sweet Potato	■	S
Asparagus			Almond			Solonaceae		
Banana			Cherry			Tomato		
Ginger			Apricot	■		Potato		
Juglandaceae			Plum			Egg Plant		
Walnut			Peach		S	Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea			Pumpkin		
Swiss Chard			Lima bean		S	Squash		
Beet			Kidney bean	■		Cantaloupe		
Spinach	◢		Lentil	■		Cucumber		
Cruciferae			Peanut			Watermelon		
Radish			String bean		S	Compositae		
Turnip	■		Rutaceae	■		Lettuce		
			Lemon		S	Artichoke		

Case 7.

on discussing the possibility of food group reactions he volunteered the information that radish, turnip, cabbage, Brussels sprouts, and cauliflower caused indigestion. So far as he knew, mustard did not disagree. He was not tested with the group extracts.

CASE 9 shows what may be but a coincidence. The patient suffers from migraine, gave a positive reaction to the leguminosae, and to one of the individual members, and has found that some of them cause migrainous attacks. She has also discovered that migraine follows the eating of honey. It is of interest that clover belongs among the leguminosae. I have not had the opportunity of testing her out with clover pollen.

Food	Reactions	Symptoms
Wheat		
Rye		
Barley		
Oat		
Rice		
Corn		
Cocoanut		
Pineapple		
Liliaceae		
Onion		
Garlic		
Asparagus		
Banana		
Ginger		
Juglandaceae		
Walnut		
Pecan		
Chenopodeaceae		
Swiss Chard		
Beet		
Spinach		
Cruciferae		
Radish		I
Turnip	■	I

Food	Reactions	Symptoms
Cabbage	■	I
Cauliflower		I
Mustard		
Rosaceae		
Blackberry		
Strawberry		
Raspberry		
Pomaceae		
Apple		
Pear	◢	
Drupaceae		
Almond	◢	
Cherry		
Apricot		
Plum		
Peach		
Leguminosae		
Pea		
Lima bean		
Kidney bean		
Lentil		
Peanut		
String bean		
Rutaceae		
Lemon		

Food	Reactions	Symptoms
Orange		
Grapefruit		
Grape		
Okra		
Cocoa		
Umbelliferae		
Parsley		
Celery		
Parsnip		
Carrot		
Sweet Potato		
Solonaceae		
Tomato		
Potato		
Egg Plant		
Coffee		
Cucurbitaceae		
Pumpkin		
Squash		
Cantaloupe		
Cucumber		
Watermelon		
Compositae		
Lettuce		
Artichoke		

Case 8.

Food	Reactions	Symptoms
Wheat		
Rye		
Barley		
Oat		
Rice		
Corn	■	
Cocoanut		
Pineapple		
Liliaceae	■	
Onion		
Garlic		
Asparagus		
Banana		
Ginger		
Juglandaceae		
Walnut		
Pecan		
Chenopodeaceae	■	
Swiss Chard		M
Beet		M
Spinach	◢	M
Crucuferae	■	
Radish		
Turnip		

Food	Reactions	Symptoms
Cabbage		
Cauliflower		
Mustard		
Rosaceae		
Blackberry		
Strawberry		U
Raspberry		
Pomaceae	◢	
Apple	■	M
Pear		
Drupaceae	◢	
Almond		
Cherry		
Apricot		
Plum		
Peach		
Leguminosae	■	
Pea		M
Lima bean		M
Kidney bean	■	M
Lentil		
Peanut		M
String bean		M
Rutaceae		
Lemon		

Food	Reactions	Symptoms
Orange		
Grapefruit		
Grape		
Okra		
Cocoa		
Umbelliferae	◢	
Parsley		M
Celery		M
Parsnip	■	M
Carrot		M
Sweet Potato		
Solonaceae	◢	
Tomato		
Potato		
Egg Plant		
Coffee		
Cucurbitaceae	◢	
Pumpkin		
Squash		
Cantaloupe		
Cucumber		
Watermelon		
Compositae		
Lettuce		
Artichoke		

Case 9.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat	■		Cabbage			Orange		
Rye			Cauliflower			Grapefruit		
Barley			Mustard		U	Grape	■	
Oat			Rosaceae			Okra		
Rice			Blackberry			Cocoa	■	U
Corn			Strawberry			Umbelliferae		
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae			Celery		
Liliaceae	■		Apple			Parsnip		
Onion	◢		Pear			Carrot		
Garlic			Drupaceae	■		Sweet Potato		
Asparagus			Almond	■		Solonaceae	■	
Banana			Cherry	◢		Tomato	■	U
Ginger			Apricot	■		Potato		
Juglandaceae			Plum	■		Egg Plant	■	
Walnut			Peach	■	U	Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea			Pumpkin		
Swiss Chard			Lima bean			Squash		
Beet			Kidney bean			Cantaloupe		
Spinach			Lentil			Cucumber		
Cruciferae	■		Peanut			Watermelon		
Radish	◢		String bean			Compositae	■	
Turnip	■	U	Rutaceae			Lettuce	■	
			Lemon			Artichoke		

Case 10.

Food	Reactions	Symptoms	Food	Reactions	Symptoms	Food	Reactions	Symptoms
Wheat	◢		Cabbage		I	Orange	◢	
Rye	■		Cauliflower			Grapefruit		
Barley	■		Mustard	◢		Grape		
Oat	◢		Rosaceae			Okra		
Rice	◢		Blackberry			Cocoa		
Corn		I	Strawberry			Umbelliferae	■	
Cocoanut			Raspberry			Parsley		
Pineapple			Pomaceae	■		Celery		
Liliaceae			Apple	■		Parsnip		
Onion	◢		Pear			Carrot		
Garlic			Drupaceae	■		Sweet Potato	◢	
Asparagus			Almond			Solonaceae		
Banana	■		Cherry			Tomato		
Ginger			Apricot			Potato		
Juglandaceae			Plum			Egg Plant	■	
Walnut			Peach			Coffee		
Pecan			Leguminosae			Cucurbitaceae		
Chenopodeaceae			Pea	◢		Pumpkin		
Swiss Chard			Lima bean	■		Squash		
Beet			Kidney bean	■		Cantaloupe	◢	
Spinach			Lentil			Cucumber		
Cruciferae			Peanut	◢		Watermelon	◢	
Radish			String bean			Compositae		
Turnip			Rutaceae	■		Lettuce	◢	
			Lemon			Artichoke		

Case 11.

CASE 10 shows quite strikingly the association of allergic manifestations with positive group reactions and with nonsymptomatic positive reactions among other members of the group.

Unfortunately, however, the results of testing are not consistently satisfactory. We have seen such a large number of positive group reactions in which the patient has been unable to demonstrate correlated symptoms from members of these groups, that we suspect that some of our reactions are nonspecific. However, we have had the same experience with a correspondingly large number of individual food reactions, and this appears to have been the experience of others.

CASE 11, that of a man with mucous colitis, may be cited as an extreme example of this. In spite of many positive and borderline reactions, which would indicate the existence of a true allergy, the only two foods producing symptoms gave rise to no positive skin reactions. We have occasionally observed positive individual reactions with associated symptoms in which the corresponding group reactions were negative (see Case 7).

It is of interest to note that the symptoms produced by the foods in this study are predominantly gastro-intestinal or cutaneous, either eczema or urticaria.

I feel that we are justified in concluding from these observations that food allergens should be classified biologically as is now being done with pollen allergens, and there is not infrequent evidence of multiple reactivity to members of individual groups; that given a positive reactor in a group, other members of the same group may sometimes produce symptoms even though their skin reactions have been negative; that the use of mixed allergens from the same group for intradermal food testing is logical and enhances diagnostic accuracy. This group testing should be adjunct to, and should not supplant individual testing.

Our knowledge of systemic botany would lead us to expect more frequent evidence of cross sensitization in some groups than in others, for the size of the families varies greatly. Thus, in the lily family there are about 300 species. In the mustard family there are about 200 genera and 1800 species. Among the rosaceae we find 75 genera and 1,200 species. The apple family is relatively small, with 20 genera and 500 species. The pea family is larger with 325 genera and over 5,000 species. The carrot family, in which crossed reaction is rather frequent, contains about 250 genera and probably 2,000 species. In the potato family there are about 75 genera and 1,750 species. The chicory family, usually placed among the compositae, contains 70 genera and about 1,500 species. We have stated that so far we have found little evidence of crossed sensitization with the commoner pollens belonging to the respective families. When we realize the large number of species in each of the groups, this is readily understood.

The evolutionary history of the food plants also helps us to understand why some are more likely to show crossed reactions than others. Among the solanaceae, for example, tomato and Irish potato both originated in the region of Chile and Peru and it is possible that they were derived from a common ancestor. Eggplant, on the other hand, although placed in the same botanical group, first appears in history in about 500 or 600 A.D., at which time it is recognized as having existed in Egypt and in China. We should state, however, that potato and tomato have shown infrequent crossed reactions.

With the exception of radish, the cruciferae enumerated in our lists are supposed by some botanists to have been derived from three species and by others from one ancestral plant. Their original habitat was Eastern Europe and Asia, and they formed a part of the dietary of the ancients before the time of Christ.

Chard was known to the ancients and was described by Aristotle, Theophrastus, Dioscorides, and by Galen. The first record of the beet appears in Europe in the second or third century. The origin of spinach, another member of the chenopodiaceae, is rather more obscure. It appears to have been a new food in Europe in the sixteenth century, but was old in China in the seventh or eighth.

While wheat, rye, and barley may all have been derived from the einkorn of Asia Minor, one would not expect these to show a crossed relationship to Indian corn, which is indigenous to Mexico and North America.

The clinical findings herein recorded serve to confirm the few chemical and immunologic observations that have been made on the proteins of vegetables.

Wells and Osborne have found that "chemically similar proteins from seeds of different genera react anaphylactically in animals sensitized with one another, while chemically dissimilar proteins from the same seed in many cases fail to do so." They conclude that the specificity of the anaphylaxis reaction depends upon the chemical structure of the protein molecule.

Gortner and Hoffman divide the proteins of the cereal grains into a "wheat group" and a "corn group." Wells finds the alcohol soluble proteins or prolamines of wheat and rye (gliadin) and of durum, einkorn, emmer, and spelt, all members of the wheat group, to be very closely related, apparently identical according to all immunologic tests applied. These prolamines, however, are not similar to those of the corn group. Hordein of barley is chemically similar to, but not identical with gliadin of wheat and rye, and immunologically is related to but distinguishable from gliadin.

The leguminous seeds contain two globulins, different chemically and immunologically, but the globulins of different legumes may be very

similar or identical. The legumins obtained from vetch, lentil, and horse bean appear to be chemically and immunologically identical.

Jones and Wells have demonstrated that the globulin from the seeds of cantaloupe and of cucumber are chemically, crystallographically, and immunologically identical (see Case 6, above).

Hawk and Bergeim state that the globulin amandin is found both in almond and in peach kernel (see Case 2).

So we find that the problem of biologic food grouping is further complicated by the fact that each food has several different proteins and in varying amounts. Assuming that protein is an allergenic factor in food allergy, the members of a biologic food group that will cross react, will therefore depend upon their qualitative and quantitative protein content. Minor variations in the protein molecular structure incident to evolutionary development may not prevent cross sensitization, since there is evidence that only certain portions of the protein molecule exert a sensitizing action. Finally, we must also recognize that the qualitative and quantitative protein make-up of one portion of a plant may vary from that of another portion of the same plant. When, therefore, we are comparing leafy vegetables with root vegetables, seeds, flowers, fruits, and stems or tubers, we may anticipate some protein variation. McCollum and Simonds recognize this possible variation in protein make-up when they state that "The proteins of the leaves appear to supplement the proteins of the seeds."

CONCLUSIONS

Clinical evidence is presented confirming the chemical and immunologic evidence of similarity or identity among proteins or allergens of different members of food groups.

A biologic grouping of food extracts for sensitization tests is proposed. The advantage of this grouping lies in more accurate systematization and in showing that other members of a food group, even though negative to test, may be responsible for symptoms.

The use of food-group test solutions at times enhances diagnostic accuracy. The group tests as described should supplement, rather than supplant, individual tests.

The results of this study suggest an explanation for apparently false negative reactions to foods which are known to produce symptoms. Such foods often fall into groups to which the subject shows evidence of sensitization.

Where some members of a group give reactions, the other members, although negative, should be watched carefully, as possible symptom-producers.

When the so-called "elimination diet" is employed therapeutically, genetic relationships should be taken into consideration in selecting the appropriate diet for the individual.

REFERENCES

Britton, N. L., and Brown, A.: An Illustrated Flora of the Northern United States, Canada, and the British Possessions, 1913, Scribner's, New York.
Robbins, W. W.: The Botany of Crop Plants, 1924, Blakiston, Philadelphia.
Hedrick, U. P.: Sturtevant's Notes on Edible Plants, State of New York Department of Agriculture, twenty-seventh annual report, Volume 2, part 2, 1919, Lyon, Albany.
Wells, H. Gideon: The Chemical Aspects of Immunity, 1929, The Chemical Catalogue Company, New York.
Wells, H. G., and Osborne, O.: J. Infect. Dis. **19:** 183, 1916.
Jones and Gersdorff: J. Biol. Chem. **56:** 79, 1923.
Lewis and Wells, H. G.: J. Biol. Chem. **66:** 37, 1925.
Hawk, P., and Bergeim: Practical Physiological Chemistry, 1926, Blakiston, Philadelphia, p. 158.
McCollum and Simonds: The Newer Knowledge of Nutrition, 1925, Macmillan, New York, p. 141.

707 MEDICAL ARTS BUILDING.

(*For discussion, see page 455.*)

THE SIGNIFICANCE OF LOCAL REACTION IN THE SKIN FOLLOWING DEEP AND SUPERFICIAL INJECTIONS OF POLLEN EXTRACTS*

LESLIE N. GAY, M.D.
BALTIMORE, MD.

FOR a number of years there has been an impression in the minds of many men interested in the treatment of pollen sensitive patients that subsequent doses of a specific extract should depend upon the se-

NAME	EXTRACT	POLLEN CONCENTRATION 1 - Grams.	DIAGNOSTIC REACTIONS DILUTIONS 1:100,000	(INTRADERMAL) 1:10,000
J. F.	Rackemann	to 100cc. Coca Solution)	Redness - 4.5 Wheal - 0.9	6.0 1.3

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	Wheal	LEFT ARM (Superficial) Redness	Wheal.	DURATION OF REACTIONS
2/5	0.1	1:10,000 (0.2cc.)	0	0	3.0	0	0
2/7	0.3	1:10,000 (0.6cc.)	slight	0	7.0 2.5		8 Hrs.
2/12 2/14 2/19			0 0	0 0	Reaction After Each Treatment		
2/21	0.5	1:1000 (1.0cc.)	0	0	7.0 2.5		72 Hrs.
2/26		Reports Extreme Discomfort in the left Arm. For Hours Arm was swollen like a "Boil". Intense Itching Preventing Sleep.					

Chart I†.

*From the Protein Clinic of the Medical Department of the Johns Hopkins Hospital.

†These ten charts demonstrate the difference in local reaction after deep and superficial injections of pollen antigens. The figures indicate diameters in centimeters.

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verity of the reaction at the site of the previous injection. Several investigators go so far as to state that they desire a severe local reaction, believing that the occurrence of a large wheal surrounded by erythema indicates the ultimate success of treatment. For example, Rackemann[1] states: "Further doses are given subcutaneously at intervals of five to seven days in amounts which depend entirely upon the local reaction to the previous dose, the object being to produce each time a local reaction with redness, swelling, and itching, varying in size from one to two inches in diameter, which reaches a maximum in about twelve hours. If the last local reaction was very small, the next

NAME	EXTRACT	POLLEN CONCENTRATION 1 : grams	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
M. L.	Rackemann to 100 cc. Coca Solution		Redness - 3.0	5.5
			Wheal - 1.0	1.2

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	RIGHT ARM (Deep) Wheal	LEFT ARM (Superficial) Redness	LEFT ARM (Superficial) Wheal	DURATION OF REACTIONS
2/7	0.3	1:10,000 (0.6cc)	0	0	0	0	
2/12	0.6	" (1.2cc)	0	0	0	0	
2/14	0.1	1:1000 (0.2cc)	0	0	4.0	1.0	
2/19	0.25	" (0.5cc)	0	0	6.0	2.0	12 Hrs.

Chart II.

dose is often doubled, but if the last reaction was larger than two inches in diameter, the next dose is not increased at all."

My experience with this method of treatment has led me to form contrary views. In rare instances patients who have received an injection of specific pollen extract have shown a severe local reaction. When such a reaction has occurred, I have thought that it resulted from an injection given partially into the true skin or just subcutaneously, when the needle entered the skin at too acute an angle. The extent of the reaction has not seemed to depend upon the volume or concentration of the material injected. The following experiments are planned to test the correctness of this hypothesis.

EXPERIMENTAL WORK

1. Extracts of ragweed pollen were obtained from Doctors Rackemann, Spain, Brown, and the Johns Hopkins Clinic. Three of the extracts were prepared by extraction with Coca solution; one was extracted with a mixture of Coca solution and glycerin.

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
L.B.	Brown	5 grams to 100cc Glyc. + Coca Solution.	Redness - 3.5	5.5
			Wheal - 1.0	2.0-Ps.

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	RIGHT ARM (Deep) Wheal	LEFT ARM (Superficial) Redness	LEFT ARM (Superficial) Wheal	DURATION OF REACTIONS
2/5	0.1	1:10,000 (0.2cc.)	0	0	0	0	0
2/7	0.3	" (0.6cc.)	0	0	5.5	0.7	0
2/12		———	0	0	Reaction After Each Treatment		
2/14		———					
3/5		———					
3/7		———					
3/12		———	0	0			
3/14	0.7	1:1000 (1.4cc.)	0	0	9.0	3.0	24 Hrs.

Chart III.

POLLEN CONCENTRATION OF EXTRACTS

Rackemann	1 gm. pollen to 100 c.c. Coca solution.
Spain	3 gm. pollen to 100 c.c. Coca solution.
Johns Hopkins	5 gm. pollen to 100 c.c. Coca solution.
Brown	5 gm. pollen to 100 c.c. of a mixture of Coca solution with glycerin.

2. A group of nine patients sensitive to ragweed pollen and one patient sensitive to timothy pollen were the subjects of this investigation.

Of the ten patients, two were treated with Brown's extract, two with Rackemann's extract, three with Spain's extract, and three with the extract prepared in the Johns Hopkins Hospital.

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
J. D.	Brown	5 grams to 100 cc. Glyc. + Coca Solution.	Redness - 4.5 cc. Wheal - 1.5 cc.	6.5 cc. 1.5 cc.

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	Wheal	LEFT ARM (Superficial) Redness	Wheal	DURATION OF REACTIONS
2/5	0.1	1:10,000 (0.2 cc.)	0	0	0	0	0
2/7	0.3	" (0.6 cc.)	0	0	4.0	1.5	2 Hrs.
2/12 2/14 2/19 2/21			0	0	Reaction After Each Treatment		
2/26	0.5	1:1000 (1.0 cc.)	0	0	6.0	2.5	24 Hrs.
2/29							
3/4	0.9	" (1.8 cc.)	0	0	7.0	5.0	48 Hrs.
3/12	0.1	1:100 (0.2 cc.)	0	0	4.5	1.0	24 Hrs.

Chart IV.

3. *Technic of Treatment.*—Into the right deltoid region, 0.1 c.c. of 1:10,000 solution of extract was injected as the initial dose. A 5/8 inch 25 gauge needle was used. With the least possible delay an equivalent amount of the same extract was injected into the left deltoid region, using in this arm a 3/8 inch 25 gauge needle. The difference in the tech-

nic was the angle at which the needle was inserted. In the right arm the long needle entered the deltoid muscle at an angle of approximately 45 degrees, while in the left arm the short needle was inserted at an angle of approximately 20 degrees, so that the solution accumulated in the true skin and in the loose subcutaneous tissue. Subsequent doses were given in the same manner in increased amounts every three to six days until sufficient data was accumulated for the study of the problem.

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
R.S.	Spain	3 grams. to 100 cc. Coca Solution.	Redness - 3.0	5.0
			Wheal - 1.2	1.5

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	Wheal	LEFT ARM (Superficial) Redness	Wheal	DURATION OF REACTIONS
2/5	0.1	1:10,000 (0.2cc.)	0	0	5.0	0	48 Hrs.
2/7	0.3	" (0.6cc.)	0	0	7.5	2.5	72 Hrs.
2/12	0.6	" (1.2cc.)	0	0	9.0	4.0	4 Days.

Returned after 4 Days. Arm Swollen Red and Hot.

Chart V.

DISCUSSION

Comparison of the twenty arms shows that the reactions in the ten right arms were insignificant. In every instance, however, the ten left arms reacted to the treatment in a most striking manner. The patients experienced considerable local discomfort, characterized by extensive edema and erythema, which persisted for as long as four days in several

instances. The error in determining subsequent dosage by local reaction is demonstrated by patients "L. T." and "S. F."

"L. T." had been given timothy treatment during the entire winter and had reached a dose of 0.9 c.c. of 1:10 dilution. "S. F." was sensitive to ragweed pollen and had received treatment during the winter,

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
M. F.	Spain	3 grams. to 100 cc. Coca Solution	Redness - 3.0	5.5
			Wheal - 1.0	1.5

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS.	LOCAL REACTIONS. (DEEP) RIGHT ARM Redness	Wheal	(Superficial) LEFT ARM Redness	Wheal	DURATION OF REACTIONS
2/12	0.3	1:10,000 (0.6cc)	0	0	4.0	0	
2/14	0.5	" (1.0cc.)	0	0	7.0	1.0	48 Hrs.
2/19							
2/21							
2/26							
2/28							
3/5	0.7	1:1000 (1.4cc)	1.0	0	7.0	3.0	72 Hrs.

Chart VI.

reaching a dose of 0.9 c.c. of 1:100 dilution. These patients had received treatment with the longer needle and without appreciable local reaction. In the experiment, however, the shorter needle produced violent local reactions in the left arm in spite of the reduction which was made in both the volume and concentration of the pollen extract injected.

POSSIBLE EXPLANATION OF THE DIFFERENCE IN REACTION

Just as chemists must not overlook the delicacy of immunologic reactions, so immunologists must not ignore the complicated anatomy of the skin. Briefly, the layer in which we are particularly interested is the true skin or cutis vera. The cutis vera is covered by the nonvascular cuticle, and is attached to the parts beneath by a layer of areolar

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
DA	Spain	3 grams to 100 cc Coca Solution	Redness - 0.5	2.5
			Wheal - 0.0	0.8

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	RIGHT ARM (Deep) Wheal	LEFT ARM (Superficial) Redness	LEFT ARM (Superficial) Wheal	DURATION OF REACTIONS
2/5	0.5	1:10,000 (1.0cc.)	0	0	2.5	0	2 Hrs.
2/12 2/14 2/19 2/21 2/26 2/28		—— —— —— —— —— ——	Treatment given without Reaction in either Arm of any Degree				
3/12	0.2	1:100 (0.4cc.)	0	0	4.0	2.0	Local edema 4 Hrs.
3/14	0.3	" (0.6cc.)	0	0	5.0	3.0	24 Hrs.

Chart VII.

tissue called "subcutaneous," which contains fat. The cutis vera is a sentient and vascular fibrous membrane, made up of a tough framework of connective tissue bundles. In this layer are lodged the sweat-glands, the hair follicles and the terminal expansion of the blood vessels. The arteries first divide in the subcutaneous tissue, and minute branches supply offsets to the fat clusters, sweat-glands, and hair follicles; they divide again and anastomose near the surface in subpapillary plexuses and, on reaching it, form a network of capillaries with polyg-

onal meshes. Fine looped branches pass from the superficial arteries into the papillae of the cutis vera. The veins accompany the arteries, but form more distinct anastomoses and plexuses; four venous plexuses may in some parts be recognized lying in successive planes parallel with the surface of the cutis.

Lymphatics are found in all parts. They form at least two networks, one superficial and another more deeply situated, which intercommunicate by uniting the vessels. The more superficial network, although close to the surface of the corium, is beneath a net of super-

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS DILUTIONS 1:100,000	(INTRADERMAL) 1:10,000
S. F.	J. H.	5 grams to 100 cc. Coca Solution.	Redness - 4.5 Wheal - 1.0	5.0 2.0 Ps.

TREATMENTS:

DATE	DOSAGE CC.	DILUTIONS & TOTAL DOSE. RIGHT AND LEFT ARMS	LOCAL REACTIONS RIGHT ARM (Deep) Redness	Wheal	LEFT ARM (Superficial) Redness	Wheal.	DURATION OF REACTIONS.
1/28	This Patient given 8 mos. Rx before this Exp. Maximum Dose:- 0.9-1:100						
2/5	0.1	1:10,000 (0.2cc.)	0	0	5.5	2.0	24 Hrs.
2/10 2/19		——— ———	0	0	Reaction After Each Treatment		
2/26	0.4	1:1000 (0.8cc.)	0	0	5.0	2.0	72 Hrs.

Chart VIII.

ficial capillaries; its constituent vessels are much larger than the blood capillaries. The lymphatics accompany the blood vessels, two passing commonly with each small artery and vein, and joining and anastomosing over the vessels. It is this layer which gives the severe local reaction after the injection of pollen extract.

The cutis vera and panniculous adiposus are attached to the underlying muscle structures. Although vascular and channeled by lymphatics, the dense plexuses are not encountered in the muscle tissue. The arteries accompanied by their veins enter the muscle at various points and divide into branches. These pass along the fasciculi, crossing over them and dividing more and more as they get between the finer divi-

sions of the muscle; at length they end in capillary vessels between the finest muscle fibers. So far as is known, there are no lymphatic vessels within the voluntary muscles, although there is an abundant supply in their connective tissue, sheaths, and tendons.

Sir Thomas Lewis[2] in his publication on *The Blood Vessels of the Human Skin and Their Responses,* sums up the reaction of these vessels when stimulated by antigens in the following: "The cutaneous vessels, like vessels in other situations, form an essential part of the mechanism

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000	1:10,000
G. H.	J. H.	5 grams to 100 cc. Coca Solution.	Redness - 2.5	4.0
			Wheal - 1.0	1.6

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE RIGHT AND LEFT ARMS	LOCAL REACTIONS RIGHT ARM (Deep) Redness	Wheal	LEFT ARM (Superficial) Redness	Wheal	DURATION OF REACTIONS
2/12	0.1	1:1000 (0.2c)	0	0	4.0	1.0	48 Hrs.
2/14		———					
2/26		———					
2/28	0.5	1:1000 (1.0c)	0	0	6.0	2.0	72 Hrs. with Local edema

Chart IX.

of defense against injuries of diverse kinds and, because the skin is particularly exposed to such, this mechanism is here developed in high degree. Thus, it comprises on the vascular side, as we shall see, a local nervous reflex whereby an intense vasodilatation with greatly increased blood flow is rapidly called into play, not only at the stimulated point, but at threatened points around. This power of calling forth an intense and local reflex vasodilatation with which the conjunctiva, another superficial structure, is likewise endowed, is seemingly nonexistent in deeply seated and more protected organs."

If one accepts this explanation, it seems to me that it describes quite clearly the mechanism of the reaction seen in the arms of patients treated by the more superficial method. Dale[3] goes so far as to state that the seat of poisoning in this type of reaction is in the reacting tissue cells. According to his view, "the reaction is due to the union

NAME	EXTRACT	POLLEN CONCENTRATION	DIAGNOSTIC REACTIONS (INTRADERMAL) DILUTIONS 1:100,000 1:10,000
L. T.	J. H.	5 grams to 100 cc. Coca Solution (Timothy Pollen)	Redness - Wheal - Violently Sensitive to All Grasses.

TREATMENTS.

DATE	DOSAGE CC.	DILUTIONS - TOTAL DOSE. RIGHT AND LEFT ARMS.	LOCAL REACTIONS. RIGHT ARM (Deep) Redness	RIGHT ARM (Deep) Wheal	LEFT ARM (Superficial) Redness	LEFT ARM (Superficial) Wheal	DURATION OF REACTIONS
This Patient was given 12 months Treatment before this Experiment. Maximum Dose:- 0.9 cc. 1:10							
3/12	0.5	1:10 (1.0cc)	2.0	0.5	6.0	3.0	12 Hrs.
3/14	0.6	1:10 (1.2cc)	2.5	0.6	6.0	3.0	12 Hrs.

Chart X.

of the poison introduced and the special protective substance, or immune body, previously present in these cells and formed there as a consequence of the first or sensitizing dose of poison."

For the reason that the deeper tissues are less vascular and because the reactive power of the muscle tissue is less sensitive than the more complicated structure, the skin, it seems to be a safer tissue into which antigens might be injected. The experiments presented are con-

clusive enough to make two statements: First, the deeper method of injection produces no local reaction, and I believe the danger of constitutional reactions to be less than by the superficial method, because of the fewer blood and lymph channels in the deeper structures; second, the discomfort to the patient is extreme when the superficial method is used; this reaction is not of benefit and should be avoided whenever it is possible to do so.

REFERENCES

1. Rackemann, F.: Specific Treatment of Late Hay Fever, J. Immunol. **11**: 1926.
2. Lewis, Thomas: The Blood Vessels of the Human Skin and Their Response, Shaw & Sons, Ltd., 1927.
3. Dale, H. H.: The Anaphylactic Reaction of Plain Muscle in the Guinea Pig, J. Pharmacol. and Exper. Therap. **4**: 13, 1912.

1014 Saint Paul Street.

(*For discussion, see page 475.*)

RAGWEED HAY FEVER*

Its Diagnosis and Treatment

Harry Markow, M.D., and W. C. Spain, M.D.
New York City

THAT there has been definite progress in the diagnosis and treatment of seasonal hay fever in the last fifteen years cannot be denied. That there has been a general education of the hay fever public regarding the necessity for prophylactic treatment is becoming more and more evident each year.

The progress in the diagnosis of this clinical entity has been rapid in the past. While Blakely in 1873 published a report on the diagnosis of this condition attributing it definitely to pollens, his work was apparently passed over lightly. In 1906, Heath,[1] in an attempt to prove that the cause of the seasonal attacks was some irritant in the air, perfected a bottle with an inflow and outflow tube; the former below a fluid level and the latter above. With the outflow tube in the patient's mouth, the inspired air was water filtered, and its use during an attack was accompanied by rapid relief as a result. Later, he perfected a nasal screen, covered with fine silk and worn in the nose during sleep as a filter for the inspired air, and he reported beneficial results.

In 1906, Dunbar[2] first made use of the pollens of grasses and weeds in the production of what he called an antitoxin, made by injecting pollen extract into a horse and using the horse's serum as a medium for diagnostic ophthalmic tests and also for treatment. This solution, called "pollantin," is still in use, and by using various dilutions in these tests, he determined the degree of sensitivity of the patient and the strength of the initial dose to be used in the treatment.

In 1911, Freeman[3] and Noon[4] made use of pollen "toxins" subcutaneously in the treatment and diagnosis of hay fever and this method, with some variation, has persisted up to the present time.

There has been but slight progress in the treatment of hay fever in the last decade, although, it is true, that there have been many changes in the method, preparation of the material used, and in the choice of the pollen. Extracts by Dunbar,[2] Noon,[4] Koessler,[5] Goodale,[6] Sormani,[7] Oppenheimer,[8] Loudermilk,[9] Clowes,[10] and Cooke,[11] while differing somewhat, were admittedly unstable and deteriorated rapidly. Koessler,[5] in 1914, concluded that the materials to be injected must be constantly of uniform potency, and that no extracts could be constant if older than three weeks. It is evident, therefore, that a solution must not

*From the Department of Medicine, Division of Immunology New York Post Graduate Medical School and Hospital, New York City.

only be potent, but must remain so during the entire course of treatment in a given season. In 1921, Coca[12] prepared a pollen extract similar to that which is now being used at this clinic, and which has been found to be stable and potent throughout the season. The importance of this contribution to the diagnosis and treatment of hay fever cannot be overestimated; it has been one of the greatest advances in the treatment of hay fever.

Hay fever, a form of allergy, is generally limited in its symptom-complex to the upper respiratory tract and eyes. It is characterized by the sudden appearance of what is commonly called a head cold; namely, congestion of nose and eyes, spasms of sneezing recurring many times during the day or night, itching of the eyes, and a puffiness appearing about the eyes which becomes aggravated by rubbing. These symptoms are seasonal in appearance, corresponding to the period of pollination of certain trees, grasses, and weeds. It occurs in the three major seasons: the spring season, corresponding to the pollination of trees; the early summer season, corresponding to the pollination of grasses and weeds; and the late summer season, corresponding to the pollination of certain weeds and flowers. When extending beyond these seasonal limits, the condition is not one of hay fever, although it may still be allergic in character. Of these three seasons, hay fever is most common in the late summer season, which begins about the middle of August, and lasts until the first killing frost. In this paper, only the late summer season is considered.

There are many plants that pollinate during the late summer season and each may be a causal factor. However, from experience with previous years' tests and treatments, the most important is the ragweed plant, and at the present time its pollen alone is used in our treatment of late hay fever. This includes both high and low ragweed pollen, and patients are found sensitive to both, so that treatment may be given with the extract of one or the other, or both, with similar results. Brown,[13] and later Spain and Hopkins[14] showed that cases of hay fever under treatment with either high or low ragweed pollen extract could be switched to the opposite extract without any harmful results no matter how high the dosage was at the time. There may be an occasional case where other plants can be definitely found to be the cause of the symptoms, but this is the exception rather than the rule. However, one must be acquainted with the various plants existing in a given locality, their season of pollination, whether wind or insect pollinated, and the abundance of the pollen in the air during the season.

A special study was made of the late hay fever cases because of their preponderance in number, and also because the public has been educated to recognize this condition and to report yearly for treatment. Two hundred cases of late hay fever were admitted to the clinic in 1929,

of which 136 received treatment sufficient to control their symptoms and to be classified. The remaining 64 cases were divided as follows:

26 were admitted after August 15.
20 had insufficient prophylactic treatment.
18 had no treatment after diagnosis.

These cases were classified, but are not reported in this paper.

SEX

The patients were about evenly divided as to sex—104 males and ninety-six females. It is surprising to see the preponderance of males in any clinic, and this speaks well for the interest of the patients in taking time out of work for relief. In 1928, the figures were 60 per cent male and 40 per cent female.

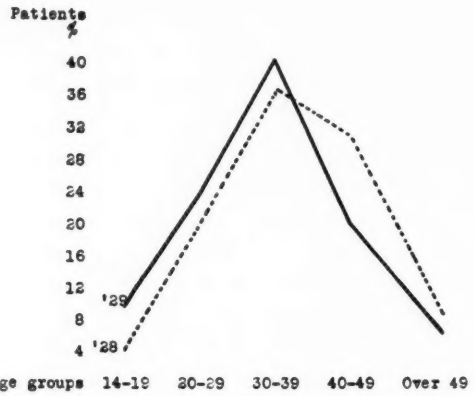

Chart 1.—Age of patients at onset of treatment.

AGE

This clinic limits the age of patients to fourteen or over; those under fourteen are admitted to the pediatric allergy clinic, and will not be considered here. Chart 1 shows that all ages are affected, most marked between the ages of thirty and fifty, corresponding to the 1928 curve. The oldest patient admitted was sixty-three years of age and several others were over fifty. The age of onset chart (Chart 2) shows that the great majority of the cases had their initial attack between the twentieth and thirtieth year, most marked between the years twenty-five and thirty-five, corresponding also to the 1928 curve. Several developed hay fever after the age of fifty; one of these began at the age of fifty-seven. Five others began at the age of six, their present ages ranging from fourteen to thirty-four. Seven began at about twelve years of age, and their present ages range from twenty-four to forty-nine. Eight cases in which the duration of hay fever extended for thirty years or more had an age of onset of twelve or less. From

these findings it seems that an early age of onset of hay fever predisposes to a long duration of the condition.

Chart 3 shows the duration of symptoms in years. In 1928, there were but 3 cases of one year's duration; in 1929, there were 31 such cases, the greatest number showing a duration of three to ten years. One patient had hay fever for thirty-seven years, and two others for thirty years. In 1928, there was one patient who had had hay fever for forty-two years. There were also a great number of new patients having their initial attacks on admission and these were treated phylactically.

FAMILY HISTORY—THE INHERITANCE FACTOR

An allergic history could be elicited in only 45 patients, or 23 per cent, of the 200 cases studied. Of these cases 27, or 13 per cent, gave a positive family history of asthma. In 13 of these cases the father had

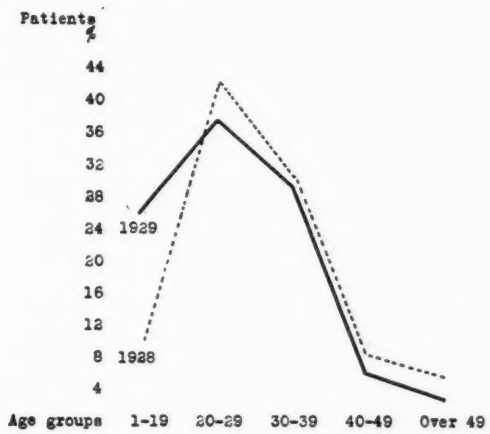

Chart 2.—Age at onset of clinical symptoms.

asthma; in 3 the mother; collateral in 4 cases; in 2 the grandparents. Four cases had a history of asthma in two members of one family.

Seventeen patients, or 18 per cent, gave a positive family history of hay fever; paternal in 3, maternal in 4, and collateral in 9. In 9 cases, hay fever was present in two or more members of one family. One case gave a family history of eczema.

These figures are admittedly incomplete. Cooke and Vander Veer[15] in a study of 504 nonclinic cases of hay fever and asthma found the family history positive for some form of clinical hypersensitiveness in 48 per cent; Spain and Cooke[16] in a similar study of nonclinic cases, but with the findings restricted to the presence of hay fever or asthma, demonstrated a positive family history in 270, or 58 per cent. June Adkinson[17] and Balyeat[18] have reported like results. It should be explained that in this study the majority of the patients were either im-

migrants themselves, or removed from this condition by only one or two generations. Positive knowledge, therefore, of the other members of their families, both antecedent and collateral, could not be expected of them. Furthermore, the condition of late hay fever here studied does not generally occur in the countries of their origins. Hence, it is realized that our figures carry no weight, since the family history cannot be satisfactorily studied in a clinic such as ours.

PREVIOUS SURGICAL HISTORY—NOSE AND THROAT FACTOR

A great number of hay fever patients are seen early by the nose and throat specialist. In many, recent operations were performed just prior to the onset of, or during the early years of, hay fever. The most frequent was the removal of tonsils and adenoids. Turbinectomies were done in many others. The following list emphasizes the fact that nasal surgical intervention should be postponed until the patient has had the benefit of at least one or more years of pollen treatment.

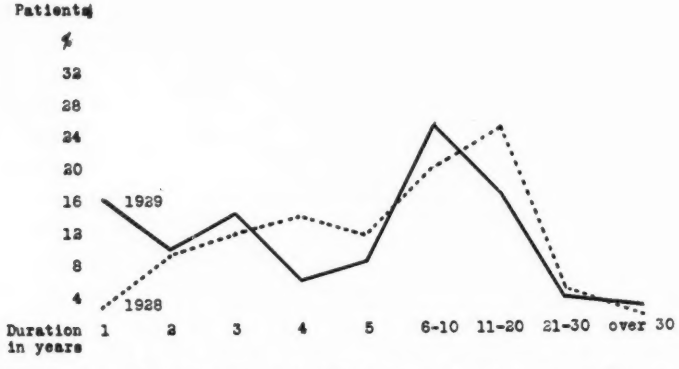

Chart 3.—The number of seasons that hay fever symptoms have been present.

Tonsils and adenoids	38 cases
Turbinectomies	20 cases
Septums	10 cases
Adenoids	7 cases
Polyps	8 cases
Sinus operation	1 case

The infected sinus cases, complicating hay fever, should be treated immediately upon diagnosis. Any operative work should be done either before or after the hay fever season.

TESTING AND CLASSIFICATION

After a complete history, a patient is tested with extracts of the pollens suggested as possible factors by the seasonal limits of the symptoms. As a rule, the history will rule out some pollens and include others. This being a review of the late hay fever season, the patients

were all tested with ragweed pollen extract, but timothy and plantain pollen extracts were also tested in each patient, and where positive were considered as potential causes of hay fever, even in the presence of a negative clinical history of early symptoms.

The ragweed pollen extract obtained by the Coca method will show a nitrogen content of about 0.3 to 0.5 mg. of nitrogen per c.c.* From this, dilutions are made of 0.1, 0.05, 0.01, 0.001, and 0.0001 mg. of nitrogen per c.c. The diagnostic tests are done intracutaneously, as this is the most delicate method. The tests are made on the outer surface of the arm with the usual sterile precautions. Approximately one one-hundredth c.c. of the 0.0001, and 0.001 dilutions are injected intracutaneously, and after ten minutes, a similar amount of the 0.01 dilution is injected, if the previous tests are negative or only mildly positive. A positive reaction is represented by an irregular wheal of varying size surrounded by an area of erythema. Itching of the site is a frequent early sign of a positive reaction. If negative to the 0.01 dilution, a test with 0.05 is tried on the following clinic day, but it is usually unnecessary to test with any stronger dilution than this. As reactions to this are often marked and difficult to control, patients failing to give a reaction to this strength cannot be considered to be ragweed sensitive.

Patients are then classified, according to Vander Veer (Table I) according to the degree of the reactions to the various dilutions of the extracts into classes AA, A, B, or C.†

TABLE I

AA	A	B	C
0.00001 marked‡	0.0001 marked	0.001 marked	0.001 moderate
0.0001 marked plus	0.001 marked plus	0.01 marked plus	0.01 marked

A reaction is marked or moderate depending upon the size and outline of the wheal and the amount of erythema. A wheal greater than one inch in diameter is considered marked plus. Classes AA and A are very sensitive; B and C are less sensitive. Since the degree of skin sensitivity is not always an indication of the degree of general sensitivity, the above classification cannot be followed blindly; but variations are necessary in individual cases depending upon their response to treatment from week to week. Just as much care must be exercised

*Hereafter, in referring to dilutions of pollen extracts it will be understood that the figures refer to mg. of nitrogen per c.c.

†This classification is practically that described by Vander Veer, Cooke and Spain in the *American Journal of Medical Sciences* **174**: 101, 1927.

‡In discussing reactions the following will be kept in mind: A negative reaction is one which shows no increase in size of the original wheal with slight or no erythema. A slight reaction shows a slight increase in size of the original wheal with moderate erythema. A moderate reaction shows an increase in size of the original wheal two or three times with a definite area of erythema. These reactions are all round wheals with no irregularity. A marked reaction shows a large wheal, irregular in outline, with pseudopods, and an area of erythema of varying size. A marked plus reaction is at least one and one-half inches in diameter.

in the treatment of the B and C cases as of the A cases. Of the cases reported, the class division was as follows:

TABLE II

CLASS	AA	A	B	C
No. of cases	1	33	89	37
Per cent of cases	0.6	20	56	24

TREATMENT—PROPHYLACTIC

Having determined the class of sensitivity of the patient, the initial dose and the subsequent doses for each class are outlined in Table III.

TABLE III

INJECTION	AA	A	B	C
Day of test	0	0	0	0.0001
1	0.00005	0.0001	0.0001	0.0002
2	0.0001	0.0002	0.0002	0.0004
3	0.0002	0.0003	0.0004	0.0007
4	0.0003	0.0005	0.0007	0.001
5	0.0005	0.0007	0.001	0.002
6	0.0007	0.001	0.002	0.004
7	0.001*	0.0015	0.004	0.007
8		0.002	0.007	0.01
9		0.003	0.01	0.015
10		0.004	0.0125	0.02
11		0.006	0.015	0.03
12		0.008	0.02	0.04
13		0.01*	0.025	0.05
14			0.03	0.06
15			0.04	0.08
16			0.05*	0.1*

*This dose is continued at 4-7 day intervals during the season.

The prophylactic treatment of late hay fever should begin at least three months before the onset of the season, which begins August 15, although it varies from year to year. Injections in the clinic are given every seven days and, in this vicinity, are so regulated that the entire series is given before the onset of the season; the top dose thus reached should be continued weekly throughout the season. If the top dose of the class is reached early and is well received by the patient, higher doses should be given up to the beginning of the season. Care should be taken to question the patient as to any general symptoms. If a marked local reaction is produced with some sneezing, coryza, etc., repeat the dose at the time of the next injection or revert to the preceding dose.

In 1929, 136 cases were treated prophylactically with ragweed pollen extract consisting of equal parts of high and low ragweed, each case having received treatment sufficient for tabulation. In all, there were given 2218 injections, averaging 16 injections per case.

YEAR	NO. CASES	NO. INJECTIONS	AVERAGE PER CASE
1928	107	1528	15
1929	136	2218	16

DOSAGE

While the average number of injections was sixteen, individual patients received as high as twenty-five, and the lowest tabulated was ten. An attempt was made to run the final dosage as high as possible irrespective of class, but subject entirely to local and constitutional reactions on the part of the patients. It was evident in 1928, that the higher the top dose the better the results recorded, and inversely, the poorer results accompanied the lower final top dose for the season. The aim in any hay fever season should be the highest possible dosage with safety. Table IV shows the top dose attained for each class in both 1928 and 1929, together with the scheduled top dose for each class.

TABLE IV

		1928			
Class	*A*	*B*	*BC*	*C*	*D*
Schedule dose	0.01	0.025	0.05	0.1	0.2
Top dose attained	0.0102	0.0202		0.041	
		1929			
Class	*A*	*B*		*C*	
Schedule dose	0.01	0.05		0.1	
Dose attained	0.025	0.037		0.046	

Many Class C cases reached 0.1, or higher, but the average was kept down because the delay in starting treatment found many patients at the onset of the season with dosage of less than 0.1 and further increase was inadvisable at that time.

A single case of Class AA, with a scheduled top dose of 0.001 reached a top dose of 0.06 without any trouble, and the results in this case suggested the wisdom of high dosage.

CONSTITUTIONAL REACTIONS

This condition still remains the stumblingblock to allergists in the successful treatment of hay fever. Not only does it develop in the sensitive group, but also in the relatively nonsensitive group (Class C). It may be slight or severe, of short or long duration, and gives the practitioner many anxious moments.

The causes of constitutional reaction may be divided into four groups:

1. Too rapid increase of dose: this cause can often be avoided by careful questioning of the patient concerning any local or general reaction from the dose immediately preceding. Every constitutional reaction should be followed by the same or a diminished dose, never by an increased dose.

2. Injection directly into the vein: this is difficult to avoid. Withdrawing the plunger before injecting the extract to see if a vein has been punctured is not dependable as the gauge of the needle used is very small. This type of reaction is the quickest in onset, often developing immediately—within five minutes after the injection. If given in the outer aspect of the arm over the insertion of the deltoid muscle and into the fatty layer between skin and muscle, the injection will, with reasonable certainty, not enter a vein.

3. The substitution of a fresh extract for an old during the course of injections: Extracts in use for as short a period as one week may deteriorate through aeration caused by repeated withdrawal of doses from the vial, and by dilution with the water of sterilization remaining in the syringe after boiling. The substitution for such an extract, of one that is fresh, produces a dose stronger than was intended and may lead to a reaction.

4. Too brief an interval between doses: Coca[19] has shown that an interval of seven days is required for the elimination of pollen extract which has been injected subcutaneously into a normal individual. From Coca's findings, as well as from clinical experiences, it is evident that too brief an interval between injections may lead to a cumulative effect, and a reaction may occur although the dosage has been properly estimated.

The early symptoms of an oncoming constitutional reaction will, if watched for, put the physician on his guard. It usually begins with a dry, hacking, frequently repeated cough, together with a rapidly increasing size of wheal at the site of the injection. There may be an itching of the palm, ear, or soft palate, an early congestion of the face followed by a pallor, congestion of eyes, wheezing, and rapid, difficult respiration similar to that of an attack of asthma. At the height of the reaction, syncope may develop. The pulse is fast and small, the breathing heavy and noisy, and the appearance of the patient may become alarming. At times, the local reaction spreads to involve the entire arm, and often the sites of previous injections on either arm light up with wheals. There may be intense itching, followed by an outbreak of urticaria involving the entire body.

The treatment is instituted immediately with the onset of the first symptom, although a local reaction may not be present. A tourniquet is applied above the site of the injection or test which is responsible for the reaction and one-half to one c.c. of adrenalin chloride (1:1000) is injected subcutaneously above the tourniquet or in the opposite arm, the dose depending upon severity of symptoms. Unless improvement is apparent in the patient within five minutes, the injection is repeated. In severe cases, adrenalin may be administered by the intravenous method. As a rule, recovery is followed by no special symptoms, but occasionally patients may have mild asthmatic symptoms for several days thereafter, or recurrent attacks of urticaria or pruritis.

A constitutional reaction should usually be followed by a reduction of about 25 per cent in dose. The dose is then gradually increased with caution; and, if a constitutional reaction recurs when the dose of the first reaction is reached, the top dose for that patient should be considered to be just below the level of the dose causing repeated constitutional reactions. At times it is possible to go beyond the dose of a previous constitutional reaction, especially when due to an intravenous injection or to a too rapid increase in dose.

Table V shows the number of patients having constitutional reactions compared to the total number treated and also the total number of injections given during the 1928 and 1929 treatment periods.

TABLE V

YEAR	TOTAL NUMBER PATIENTS TREATED	NUMBER PATIENTS WITH CONSTITUTIONAL REACTION	PER CENT	NUMBER OF INJECTIONS	NO. OF CONSTITUTIONALS	PER CENT
1928	107	10	10	1581	17	1
1929	136	19	14	2218	28	1

The rate is not high and in private practice it is found to run about one reaction to every hundred injections.

Table VI shows a list of nineteen patients with the number and dose of the constitutional reactions and also the final top dose for the year. Note the effect of the constitutional reaction upon the final top dose; also, that increasing the dose after the first constitutional reaction was obtained, was soon followed by succeeding constitutional reactions which permitted no further increase in dosage. This can be listed as a fifth cause of constitutional reactions; i.e., reaching the upper limit of a patient's tolerance beyond which further increase in dosage precipitates constitutional symptoms. The results of treatment are charted according to the number of days of no hay fever, moderate hay fever, or severe hay fever. It should be noted that this group contained reactions both severe and mild.

EFFECT OF VARIATIONS IN THE WEATHER UPON SYMPTOMS

A daily record was kept from August 15 to September 30, of the symptoms in 103 cases of late hay fever treated prophylactically in 1929. The degrees of severity were designated as "severe," "moderate," and "slight or no hay fever." The cases presenting "severe" or "moderate" symptoms were grouped together, as opposed to those with "slight or no hay fever" and the daily percentage of cases falling in this group was estimated. Thus, on August 15 (see Chart 4) 4 per cent of the cases reported "moderate" or "severe" symptoms (with 96 per cent reporting "slight or no symptoms"), while on August 17, 18 per cent fell into this group (with the corresponding 82 per cent reporting "slight or no symptoms" for the day). A graph was made

TABLE VI

NO.	CHART NO.	CLASS	NO. OF REACTIONS	REACTION DOSE	DATE OF REACTION	TOP DOSE AT END OF SEASON	RESULT OF TREATMENT			SEASONAL COMPLICATIONS
							NO. SEVERE DAYS	NO. MOD. DAYS	NO. FREE DAYS	
1	289	B	2	0.006	8/ 9/29	0.004				
				0.006	8/23/29	0.004	10	19	12	Asthma 8/23 to 9/28
2	294	C	2	0.007						
				0.03	9/16/29	0.03	0	4	34	
3	321	A	2	0.025						Asthma throughout season
				0.025		0.025	0	4	28	
4	328	A	1	0.004	8/ 2/29	0.01	0	12	31	
5	508	C	2	0.004						
				0.004	8/16/29	0.003	75%	improved		No asthma. Severe last year
6	569	A	1	0.01		0.01	4	9	31	Asthma 8/28 to 9/11
7	701	A	1	0.0125	8/23/29	0.0125	1	0	40	
8	710	B	1	0.04	9/16/29	0.04	0	26	7	
9	722	B	1	0.04	9/13/29	0.04	6	9	30	
10	726	C	4	0.01						These reactions were with no local reaction and only slight general symptoms
				0.025						
				0.02	7/19/29	0.01	0	0	50	
				0.03						
11	725	C	1	0.05	9/ 9/29	0.05	10	5	21	
12	738	B	1	0.05	9/13/29	0.05	2	7	21	
13	747	A	1	0.03	9/ 9/29	0.03	4	16	16	
14	749	B	1	0.01	8/ 9/29	0.01	3	5	25	Asthma after constitutional reaction—8/9 Asthma after injection—9/6
15	754	AA	2	0.00005	6/14/29	0.06	0	0	35	
				0.0007						
16	764	C	1	0.03	9/13/29	0.03	1	0	41	
17	769	C	1	0.02	8/30/29	0.025	1	4	33	
18	633	B	2	0.004		0.08	0	0	45	
				0.015						
19	One patient had constitutional reaction after the preliminary dilution tests with ragweed extract and this patient attained the top dose of 0.025 for Class A and had a very successful season.									

of the daily mean temperature and relative humidity as obtained in Central Park, New York City, by the government Weather Bureau. The rainfall in inches was also charted. By referring to Chart 4 it will be seen that the curves for symptoms and for temperature were roughly parallel, the three peaks in severity of symptoms (August 27, September 3, 11) corresponding to the three peaks of high temperature. Furthermore, a drop in temperature was accompanied by a drop in the symptoms. A comparison of the humidity curve with the symptom curve shows that they were inversely proportional. The three peaks in the severity of symptoms occurred upon days when there was the

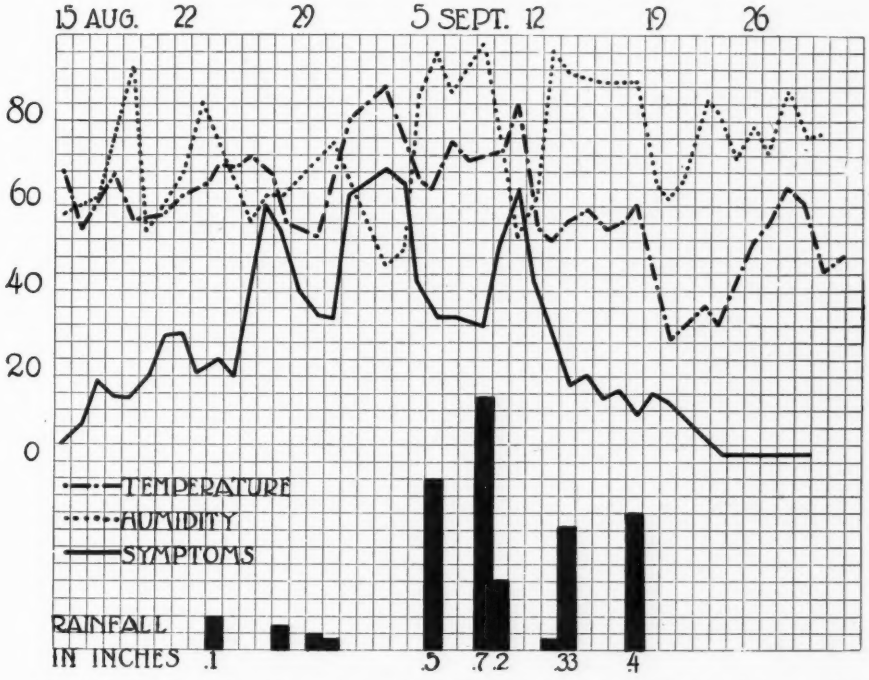

Chart 4.—The relationship between the daily variations in mean temperature, relative humidity, and symptoms, in 103 cases of late hay fever. The figures on the ordinate refer to degrees of temperature (Fahrenheit), relative humidity, and percentage of patients with severe or moderate hay fever.

greatest drop in relative humidity. As the humidity curve rose, the symptom curve would fall.

The first rainfall of any considerable degree during the late hay fever season was upon September 6, followed by a heavy rain upon September 9 and 10. From the graph it appears that not only upon the days of the downpours but also of the lighter showers, the symptoms were much less. It is realized that too definite conclusions should not be drawn from the findings of one season. It is of interest to note, however, that based upon the daily symptom record of these 103 cases it appears that the patients' discomfort from hay fever is decidedly increased upon days of very high temperature and low humidity, in

conformity with the experience general among hay fever sufferers that they are most uncomfortable upon such days. A record of the daily pollen content of the air during the late hay fever season would be interesting compared with the above findings. Such a study is in progress.

EFFECT OF TREATMENT ON SKIN REACTION

Each case was tested at the beginning of the treatment and retested one week later. This course was followed to check up on the class of each patient. Tests done at the end of the season after a complete set of treatments showed very little change in reactions. If any, the reaction to the 0.0001 solution became weaker, but the 0.001 or 0.01 tests remained unchanged. This upholds the contention that a lessening of the clinical symptoms under treatment is not reflected by the elimination of skin sensitiveness upon testing, and often a Class C patient will have a more severe season than a Class A patient. In no case did the skin reaction disappear after the series of prophylactic treatments.

TESTS WITH LATE POLLENS OTHER THAN RAGWEED

Tests were also done during the course of treatment with extracts of other late pollens, including cosmos, goldenrod, hemp, pigweed, sunflower, and corn. The 0.001 solution was first tested and if no marked reaction followed, the 0.01 solution was used. The results were as follows:

35 per cent reacted to cosmos.
20 per cent reacted to goldenrod.
8 per cent reacted to hemp.
8 per cent reacted to pigweed.
35 per cent reacted to sunflower.
7 per cent reacted to corn.

Several patients reacted to two or more of these, and some reacted to all of these. It would be of interest to learn the exact relationship between this sensitivity and the patient's symptoms, and possibly, by including one or more of these pollens in the ragweed treatments, a better result might be obtained in some cases than with ragweed extract alone.

RESULTS OF TREATMENT

It is difficult to put results down in figures; these may mean one thing to the patient and quite the opposite to the physician. Neither can the patient be relied upon for his own opinion in the matter. Cards were distributed to each patient at the beginning of the season upon which he was to indicate his condition each day of the season. This was done by marking a cross for each day under one of three columns: no hay fever, moderate hay fever, or severe hay fever. At the end of the season one could tell how many days of each the patient had experienced. It also was decided that each patient having five or less severe days during the season should be considered successfully treated.

0 severe days of hay fever—44 patients
1 severe day of hay fever—12 patients
2 severe days of hay fever— 7 patients
3 severe days of hay fever— 7 patients
4 severe days of hay fever— 8 patients
5 severe days of hay fever— 2 patients
6-10 severe days of hay fever—16 patients
11 or more severe days of hay fever— 8 patients

Thus, 80 patients could be considered successfully treated out of a possible 104 reported. Of the unsuccessful cases, one reported sixteen severe days, but was 50 per cent improved over the year before; another had ten severe days, but the top dose was only 0.006, because of two constitutional reactions; others had had insufficient treatment. These reports were checked up by the patient's own expression of results in percentage at the end of the season and the figures are as follows:

38 per cent reported 80 to 100 per cent improvement.
50 per cent reported 50 to 80 per cent improvement.
12 per cent reported an improvement of less than 50 per cent.

PHYLACTIC TREATMENT

A group of 25 patients began treatment during the hay fever season. These were tested and classified, but the treatments given weekly consisted of doses 0.0001, repeated three or four times; 0.0002, repeated three or four times, and 0.0003, repeated weekly. It is surprising to note that the results obtained in these cases were exceptionally good, but it is felt that satisfactory results can be obtained only by properly given prophylactic treatments.

SUMMARY

This paper is a review of the 1929 hay fever season at the hay fever clinic of the Post-Graduate Hospital, New York City. Two hundred patients were admitted before and during the season of which 136 received sufficient treatment for purposes of review as to the method used, dosage, type of extract used, and results. Daily charts of symptoms were kept by each patient, so that a daily average of condition could be reached for the entire group. These reports have been compared with the mean daily temperature, humidity, and rainfall, and a chart of their relationship has been drawn. Prophylactic treatment was the method of choice. Phylactic treatment was the method of necessity in a group of 25 patients. While the results in the latter were satisfactory, the method of treatment is not to be encouraged as a substitute for the prophylactic method.

CONCLUSIONS

1. Hay fever is a prominent factor in the life of a large group of individuals. Successful treatment eliminates a period of financial, social, and mental strain.

2. An extract that will remain potent throughout the season is indispensable. Such an extract, made according to the modification of Coca, has been obtained, yielding positive undiminished skin reactions throughout the season.

3. Classification of patients according to skin sensitivity will eliminate an unnecessary number of weak doses as well as some constitutional reactions. It is, however, no absolute indication of the constitutional sensitivity of the patient.

4. While the average number of injections was sixteen, the total should not be limited. The patient should be treated as long as there are symptoms.

5. Prophylactic treatment is the method of choice and allows rapid increase of dose. The top dose for the class should be reached before the onset of season, after which an increase of dose should be very gradual, depending upon previous local reactions.

6. Constitutional reactions should be watched for after each injection. Treatments should follow immediately upon the appearance of the earliest sign or symptom. Each constitutional reaction should be considered a serious complication and should be treated quickly and energetically.

7. The top dose for some patients may be increased each year when no constitutional reaction occurred the year before.

8. Of the 103 daily cards returned, 75 per cent were successfully treated; 15 per cent had moderately good results, and but 10 per cent could be considered unsuccessfully treated.

9. From the patients' viewpoint, only 2 per cent reported at the end of the season that the results were unsuccessful. All the others reported improvement of from 25 to 100 per cent.

10. These facts justify the continuation of this method of treatment as being the most effective yet devised for the relief of symptoms in hay fever.

REFERENCES

1. Heath, A. C.: J. A. M. A. **47**: 1300, 1906.
2. Dunbar, W. P.: J. Hyg. **13**: 105, 1913.
3. Freeman, J.: Lancet **2**: 814, 1911.
4. Noon, L.: Lancet **1**: 1572, 1911.
5. Koessler, K. K.: Illinois M. J. **26**: 120, 1914.
6. Goodale, J. L.: Boston M. & S. J. **179**: 293, 1918.
7. Sormani, B. P.: Lancet **1**: 348, 1916.
8. Oppenheimer, S.: New York M. J. **101**: 229, 1915.
9. Loudermilk, R. C.: J. A. M. A. **63**: 141, 1914.
10. Clowes, G. H. A.: Proc. Soc. Exper. Biol. & Med. **10**: 70, 1913.
11. Cooke, R. A.: Laryngoscope **25**: 108, 1915.
12. Coca, A. F.: J. Immunol. **7**: 163, 1922.
13. Brown, A.: J. Immunol. **13**: 73, 1927.
14. Spain, W. C., and Hopkins, M.: J. ALLERGY **1**: 209, 1930.
15. Cooke, R. A., and Vander Veer, A.: J. Immunol. **1**: 201, 1916.
16. Spain, W. C., and Cooke, R. A.: J. Immunol. **9**: 521, 1924.
17. Adkinson, June: Genetics **5**: 363, 1920.
18. Balyeat, Ray M.: J. Oklahoma M. A. **16**: 240, 1923.
19. Levine, P., and Coca, A. F.: J. Immunol. **11**: 462, 1926.

STUDIES OF BRONCHIAL SECRETION*

W. B. KOUNTZ, M.D.
AND
KARL KOENIG, B.S.
ST. LOUIS, MO.

IN THE literature almost no work has been found on the subject of the nervous control of secretion in the bronchial mucous membrane. The nearest approach is an investigation of the tracheal mucous membrane secretion which was undertaken both by Rossbach[1] and Calvert,[2] who opened the trachea of animals, wiped the mucous membranes dry, and noted the time required for the secretions to reform on the surface. Their observations were made on secretion under normal conditions, after stimulation of the vagus, and after the administration of drugs, such as expectorants, general depressants, and stimulants. They concluded that both vagal and peripheral nerve stimulation caused a shortening of the time taken for the moisture to reform on the surface of the mucous membranes but that sympathetic stimulation on the other hand lengthened the interval. Henderson[3] has also studied and recorded the effect of the same class of drugs on bronchial secretion.

Bronchial secretion may be excessive in certain clinical conditions, notably after a paroxysm of bronchial asthma, tumors, massive collapse, and foreign bodies. The determination of the nervous control of the bronchial mucous membrane may pave the way for rational therapeutic measures to counteract excessive bronchial mucus.

As far as we are aware, no one has attempted to measure or record the amount of fluid produced by the mucous membrane of the trachea or bronchi, an omission possibly due to mechanical difficulties, chief among which is the small amount normally secreted. In the following study we have tried to develop a method by which we would measure the amount of secretion per unit area of bronchial mucous membrane both normally and after stimulation of vagus and sympathetic nerves.

TECHNIC

Experiments were attempted on rabbits, cats, and small dogs but only on large dogs were the bronchi large enough to permit the easy passage of instruments. Various anesthetics were tried, but only decerebration of the animals gave constant results, and this procedure was used in our experiments. After decerebration, the animals were turned on the left side and the right scapula was deflected anteriorly and superiorly

*From The Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

and the muscles were cleared from the chest wall. Artificial respiration, if unnecessary before this time, was commenced and the blood pressure record was started. The chest was opened with an incision from 4 cm. to 6 cm. in diameter through which, when viewed from the back, the primary division of the trachea could be seen. One branch was traced into the lung tissue and isolated by means of a cautery. With the cautery also, an oval opening was made large enough to introduce an instrument and absorbing paper into the bronchus. After all bleeding was stopped and the clots were removed, the bronchus was sealed above with soft paraffin.

A modified Coleman male urethral dilator was used to introduce the absorbing paper. In order that the instrument might not come in con-

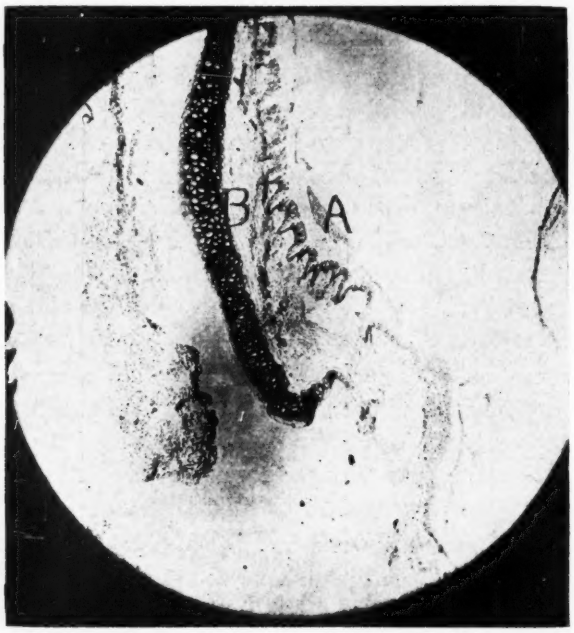

Fig. 1.—A. Secretion in lumen of bronchus. B. Bronchial wall. Secretion was seen only in animals in which the vagus was stimulated.

tact with the edges of the opening made in the bronchus, the instrument was arranged in such a way that only the end would expand. Fastened to the instrument and placed around the paper was a small interchangeable spring which conformed to the size of the dilator and facilitated removal of the paper from the bronchus. A clasp to hold the edge of the paper was attached to the point of the instrument. Absorbent paper which had been previously cut, sealed in a tube, and weighed, was then introduced through the opening into the lumen of the bronchus by means of the dilator. After introduction, the dilator was distended to the point where the paper was in close proximity to the bronchial wall. After the absorbent paper had been held in place for twenty minutes, the instrument was reduced by means of the spring to

a size sufficiently small to permit its removal. After exposure, the paper was placed in the same tube from which it had been removed. The tube was sealed and weighed.

The technic was by no means without difficulty. Control of the bleeding, which at first was the greatest obstacle, was at last completely obtained by improvement of technic, and all papers on which blood collected were discarded. The necessary artificial respiration also presented a difficulty. When it was extensive enough to support the animal, the blast of air in the bronchus caused drying of the secretions and it became necessary to plug the lumen of the bronchus above the opening in order to diminish the air passing into it.

In order to study the influence of the vagus and sympathetic nerves, these nerves were isolated in the neck and their peripheral cut ends were stimulated with interrupted currents of varying degrees. The stimulus was applied to the nerve for a period of fifteen seconds out of each minute of the experiment. After vagal stimulation, a rest period of fifteen minutes was allowed. After this, the bronchus was wiped dry and observations were repeated. At the end of the experiment, 1 per cent mercurochrome was sprayed into the bronchus and the absorbent paper was again introduced in the same manner as previously in order to determine the surface area of paper in contact with the bronchial wall. By this method, the approximate area of mucous membrane from which the secretion was obtained could be estimated.

RESULTS

Many animals were used, but the early difficulties in technic were so great that the results were not dependable. The following four experiments were performed with the best technic possible, and they represent as nearly complete results as could be obtained with the method.

TABLE I

THE NORMAL SECRETION PRODUCED IN A BRONCHUS

ANIMAL NO.	WT. OF TUBE AND PAPER (BEFORE INTRODUCTION) GRAMS	WT. OF TUBE AND PAPER (AFTER INTRODUCTION) GRAMS	SEC. WT.[1] GRAMS	ABSORBING SURFACE SQ. CM.	GM. SEC. PER SQ. CM.[2]	SEC. PER MIN. PER SQ. CM. MG.[3]
8	0.54	0.54125	0.00125	8.75	0.00014	0.07
	0.6766	0.67795	0.00135	8.75	0.00015	0.075
12	0.7450	0.7468	0.0018	8.22	0.000205	0.01025
	0.7551	0.7571	0.002	8.22	0.0024	0.012
24	0.52347	0.52372	0.00025	7.06	0.000035	0.00175
	0.73357	0.733585	0.00028	7.06	0.000039	0.00195
	0.84322	0.84248	0.00026	7.06	0.000036	0.0018
15	0.55425	0.55528	0.00103	7.84	0.00013	0.065
	0.46402	0.46482	0.00080	7.84	0.000102	0.051

[1]Secretion weight.

[2]Grams secretion per square centimeter.

[3]Milligrams of secretion per minute per square centimeter.

The amount of normal secretion and the effects of vagal and of sympathetic stimulation were studied in Dogs 8, 12, 15, and 24.

The values for the secretion in the bronchus without artificial stimulation or any disturbing factors other than the technic itself are presented in Table I.

In Table II the results of vagal and sympathetic stimulation are recorded.

TABLE II

THE EFFECT OF VAGUS AND SYMPATHETIC STIMULATION UPON THE BRONCHIAL MUCOUS MEMBRANE

DOG NO.	STIMULANT	WT. OF TUBE AND PAPER (BEFORE INTRODUCTION) GRAMS	WT. OF TUBE AND PAPER (AFTER INTRODUCTION) GRAMS	SEC. WT.	SEC. PER (SQ. CM.) GRAMS[3]	PER CENT NORMAL
8	Without stimulant				0.000145	
	R. vag.[1]	0.56310	0.56655	0.00345	0.000394	273
	R. vag.	0.67532	0.67884	0.00352	0.000413	285
	L. vag.	0.55604	0.55889	0.00285	0.00032	227
	L. vag.	0.75781	0.75	0.00219	0.00028	193
	R. sym.[2]	0.74290	0.74391	0.00101	0.000115	80
	R. sym.	0.65328	0.65408	0.00080	0.000091	63
	L. sym.	0.64590	0.64710	0.00120	0.000128	88
	L. sym.	0.59201	0.59293	0.00092	0.000105	72
12	Without stimulant				0.00022	
	R. vag.	0.77405	0.77685	0.00280	0.00034	154
	R. vag.	0.6784	0.68152	0.00312	0.000379	172
	L. vag.	0.63568	0.63901	0.00333	0.000405	184
	L. vag.	0.72317	0.72668	0.00351	0.000427	194
	R. sym.	0.64350	0.64550	0.002	0.00024	109
	R. sym.	0.71632	0.71794	0.00162	0.00019	86
	L. sym.	0.6482	0.65	0.0018	0.000218	99
	L. sym.	0.67832	0.67994	0.00162	0.00019	86
24	Without stimulant				0.000036	
	R. vag.	0.73322	0.73380	0.00058	0.000082	228
	L. vag.	0.83280	0.83336	0.00056	0.000079	219
	R. sym.	0.74322	0.74342	0.0002	0.000028	78
	L. sym.	0.56330	0.56358	0.00028	0.000039	108
15	Without stimulant				0.000116	
	R. vag.	0.7450	0.74658	0.00158	0.000216	186
	R. vag.	0.65131	0.65301	0.00170	0.000217	187
	L. vag.	0.73214	0.73394	0.00180	0.000229	197
	L. vag.	0.59220	0.5938	0.00160	0.000204	179
	R. sym.	0.65367	0.65412	0.00045	0.0000561	48
	L. sym.	0.57324	0.57390	0.00066	0.000097	84

[1]Right vagus.
[2]Right sympathetic.
[3]Secretion per square centimeter.

Following vagal stimulation, there is apparently increased secretion, while after stimulation of the sympathetic, the secretion remains normal or is even slightly diminished. With the method of investigation, the results are definite and unequivocal. The vagus apparently stimulates bronchial secretion while the sympathetic fails to influence it or may depress it.

Several objections could be urged against the method. The manipulation might cause disturbances in circulation to the bronchial mucous membrane and to the walls of the bronchi. The free bleeding which occurred from all surfaces of the wound possibly indicates that the circulation was not diminished. In a comparative study, however, it is likely that the amount of possible mechanical interference with the circulation was the same in each individual animal during the control period and after vagal and sympathetic stimulation. Mechanical irritation may also have increased the amount of secretion but this should have been approximately equal in the conditions which were compared.

A more serious objection is that the increased secretion during vagal stimulation may have been more apparent than real. It is well known that stimulation of the vagus causes constriction of the bronchus which under the experimental conditions might have brought a greater surface of mucous membrane and hence more secreting area into contact with the paper. It also seems possible that constriction of the bronchus may have, by a milking action, caused the glands to empty more completely. These possibilities cannot be entirely excluded.

Microscopic studies of the cells of the mucous membrane and the secretion were made in five dogs. Two normal animals were used, two in which the vagi were cut and stimulated, and one in which the sympathetic was stimulated. The bronchi were removed and fixed and stained with Hoyer's theocin and Delafield's hematoxylin stain. A definite increase in the amount of mucus in the cells and bronchi was noted after vagus stimulation. No change either in amount or character of the secretion was seen after sympathetic stimulation.

The work is in keeping with the clinical observation that in bronchial asthma wherein a paroxysm is known to be due to vagus stimulation, great excess of bronchial mucus is present. Both the paroxysm and mucous secretion are controlled by epinephrin and atropine which counteracts vagus action.

CONCLUSIONS

1. In the dog, the secretion per unit area of bronchial mucous membrane is apparently increased by vagal stimulation.

2. Stimulation of the sympathetic nerve in the neck causes little change or possibly a slight decrease in the amount of secretion.

REFERENCES

1. Rossbach, M. G.: Berlin, klin. Wchnschr. **19**: 281, 1882.
2. Calvert, B. A.: J. Physiol. **20**: 158, 1896.
3. Henderson, V. E.: J. Pharmacol. & Exper. Therap. **2**: 1, 1910.

600 South Kingshighway.

SUDDEN DEATH FROM BRONCHIAL ASTHMA*

JOHN A. MURPHY, M.D., AND E. A. CASE, M.D.
PHILADELPHIA, PA.

RACKEMANN'S[1] review of deaths from asthma up to 1926 found the number dying of uncomplicated asthma to be eleven. Kountz and Alexander[2] added three more and Steinberg and Figley[3] have reported two cases. Recently, Wright[4] reported another case.

Report of the case presented is made because the clinical and pathologic diagnoses are so closely in accord that death can be ascribed to an uncomplicated asthma, the immediate terminal factor being acute pulmonary emphysema, with asphyxia. The points of interest in this case are the age of the patient, thirty-one, the relatively short duration of the asthmatic dyspnea, one year and nine months, the heroic doses of adrenalin used by the patient, and the absence of any pathologic condition of the adrenal glands.

Clinical History.—M. B., female, aged thirty-one years, white, American, married, was seen September 24, 1928, and gave a primary history of hay fever, early and late types, with an onset of asthma in November, 1927. Her hay fever had spontaneously improved in recent years and prior to the first attack of asthma she had not suffered any dyspnea. There was no immediate circumstance to account for the onset. The attacks became more frequent and severe, showing decided exacerbations during the hot months and each relapse was preceded by a hay fever-like syndrome.

Family History.—No antecedent or collateral history of allergy.

Previous History.—She was married at the age of seventeen; she had three children, all of whom died in early childhood. No miscarriages or stillbirths; no serious illness and, except for the former hay fever, no etiologic basis was found for the asthmatic attacks.

Present History.—Asthmatic seizures occur from 2 P.M. to 8 A.M., being most severe after midnight and much worse during hot humid weather. Exertion did not provoke attacks but decidedly aggravated them. Milk in large quantities was demonstrated clinically as aggravating her condition, but not as an exciting factor. Overeating undoubtedly provoked attacks. She had no headaches, but noted a sense of fullness in the frontal region and occasionally had cramp-like pains in the fingers and toes, which were associated with and closely followed a dose of adrenalin.

Physical Examination.—Adult female, 5 feet, 2 inches tall, weighing 118 pounds. No abnormal anatomic defects, except a moderate bulging of the lower anterior thorax and a median postoperative abdominal scar.

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Nasal examination showed shading of the right maxillary and clouding of the left maxillary sinuses. The septum was markedly deflected to the right, with small polyps in the left middle meatus and evidence of bilateral ethmoiditis. The heart was normal in size and position; there were no murmurs, the rate being rapid but regular.

Laboratory Findings.—The urine was normal and blood studies exhibited no abnormalities; the eosinophiles were 2 per cent. The sputum showed pneumococci, Friedländer's bacillus, and yeast molds. It was not examined for eosinophiles. Protein tests showed multiple reactions of a mildly positive type to daisy, dandelion, ragweed, sunflower, cosmos, dahlia, aster, cheese, spinach, and orris root. There were suspicious readings to house dust, dog hair, goldenrod, and peach, with delayed reactions to egg white, asparagus, lima bean, and pear. Subsequent testing showed a marked reaction to orris root, a moderate one to grass pollen, and a delayed one to duck feathers. She was very skin sensitive to the respiratory bacteria, especially to Staphylococcus aureus and albus, Streptococcus hemolyticus and viridans, pneumococcus Types I and II, and B. influenzae.

An autogenous vaccine, a secretion filtrate, and a soluble toxin were prepared from her sputum after the method of Wilmer[5] and Eiman,[6] and she showed typical allergic reactions with these which persisted for twenty-four hours. Administration of the autogenous vaccine provoked slight to severe focal reactions. None was noted to the secretion filtrate and a severe one was caused by the soluble toxin.

She administered adrenalin to herself and was using from 30 to 50 injections daily, varying from 5 to 20 minims per dose, an ounce bottle frequently being used in one day.

Course.—The attacks became less frequent and less severe with the administration of the products prepared from her sputum and symptomatic treatment from September, 1928, to January, 1929, when a relapse occurred, and she was acutely and continuously ill for six weeks. A temporary ten-day complete relief followed this attack with another relapse March first. Thereafter she had comparatively mild and infrequent attacks until May, when she became much worse and resorted to the frequent use of adrenalin again. At this time, she complained of a marked sense of constriction of the throat, as though being choked, that the chest oppression had moved from the lower to the upper thorax, that one cubic centimeter doses of adrenalin caused severe headache, precordial pains, and cramp-like pains in both arms, and that at the peak of the attacks she felt as if she were being choked to death.

She had been advised to enter a hospital which she did on August 7, 1929, at 2:30 P.M. I saw her at four o'clock on this date and found her practically symptom-free. I was called one hour later and informed of her sudden death.

Pathologic Notes.—Body of a well-developed woman showing considerable postmortem lividity. Pupils equal and slightly contracted.

No other external appearance was of pathologic interest. Operative scar in midline below the umbilicus.

Peritoneal Sac: No fluid present. Adhesions were found in the region of the ovaries; the right one was missing. A long cord-like adhesion extended from the fundus uteri to the sigmoid. The large intestine was distended with gas. Pleural Sacs: No fluid or adhesions in either sac. Pericardium: The lining membrane was smooth and the fluid normal in amount and character.

Heart: Weight 215 grams. The organ was normal in size, shape, and consistency. The subepicardial fat was not excessive and the muscle tissue of good texture and firm. The valves showed no pathologic change and the coronaries had only very small yellowish patches in the intima. The aorta was small and unusually free from disease, possessing considerable elasticity.

Left Lung: Weight 360 grams. This organ was large, distended, soft and cottony to the touch, and pinkish in color. Palpation showed reduction in crepitation with no consolidations present. The emphysema was marked and involved the entire organ. The cut surface was congested but not edematous. The mucosa of the bronchi and its branches was injected; and there was a large amount of tenacious, stringy mucus present, even in the small branches. The mucus undoubtedly had interfered materially with breathing. The walls of the bronchi and the bronchioles were thickened and the structures prominent. Right Lung: Weight 435 grams; resembled the left lung.

Spleen: The spleen was soft, the pulp being congested, and the cut surface roughened.

Adrenals: Grossly these structures were normal.

Left Kidney: Weight 95 grams. It was not large; the capsule stripped easily, leaving a smooth, dark red surface. The cut surface was dark red and the markings were clear and sharp. The glomerules could be seen as minute dark red spots. The pelvic mucosa was smooth but slightly congested. The right kidney weighed 110 grams and resembled the left one. The ureters were normal in size and position, the mucosa being smooth, and there were no constrictions. They contained a small amount of purulent-looking material. The bladder was contracted and contained a small amount of thick, creamy fluid; the mucosa showed some congestion, but was smooth. The uterus was fairly large and firm. The cervical canal and the lips of the cervix were injected, otherwise the organ was normal. The fallopian tubes had been removed, together with the right ovary. There were some adhesions present in this region.

The esophagus showed no obstruction or pathologic change, the same being true of the trachea and larynx. The stomach was distended, containing considerable undigested food, and showing submucous hemorrhages. Submucous hemorrhages were noted also in the duodenum.

The colon and sigmoid were distended. The pancreas was soft and when cut it showed considerable postmortem change. The liver was large, weighing 1915 grams, and of a peculiar shape. The left lobe was larger than usual and joined the right lobe by a constricted portion leaving a deep notch on the upper and lower borders. The surface was smooth and brown as was the cut surface. The gall bladder was small and nearly empty and showed no evidence of disease. The thyroids appeared normal. The brain cavity was not opened.

Microscopic Study.—A microscopic study of the lungs showed intense congestion and hemorrhage, both in the tissues of the bronchi and the alveoli. In cross-sections of the larger branches of the bronchi, there was no epithelial lining, the cells having desquamated; consequently, the lumen contained large numbers of these cells in addition to blood and débris. In the submucosa there was a small amount of cellular infiltration of the mononuclear type. The capillaries here also showed congestion. The muscle coat was unusually prominent due to hypertrophy, and here and in the outer coat there was dense infiltration of eosinophiles. The smaller branches showed a similar picture with débris, epithelial cells, and blood corpuscles in the lumen, desquamation of the mucosa, hypertrophy of the muscle coat, congestion of the vessels, and infiltration of eosinophiles. The peribronchial lymph nodes contained an unusual number of eosinophiles in their sinuses.

The adrenals showed no morphologic change indicative of a pathologic process. There was abundance of medullary tissue and its cells stained well. The cortex was proportionate in amount and there appeared to be no structural change resulting from disease.

In the capillaries of the liver, an increase in the number of eosinophiles was evident. There was congestion and a mild degree of degeneration. The kidneys were congested and showed degeneration of the cells of the convoluted tubules. The slides from the cervix confirmed the gross diagnosis of endocervicitis.

The clinical diagnosis was bronchial asthma and death was attributed to asphyxia due to acute emphysema.

The pathologic diagnosis was acute bilateral emphysema, with obstruction of the bronchi and their branches by thick, tenacious mucus.

BIBLIOGRAPHY

1. Rackemann, F. M.: Fatal Asthma, Boston M. & S. J. **194:** 531, 1926.
2. Kountz, W. B., and Alexander, H. L.: Death From Bronchial Asthma, Arch. Path. **5:** 1003, 1928.
3. Steinberg, M., and Figley, K.: Pathology of Asthma: Nonbacterial Allergic and Bacterial Types Based on Autopsy Material, J. Lab. & Clin. Med. **13:** 921, 1928.
4. Wright, C. B.: Death From Bronchial Asthma, J. A. M. A. **94:** 1218, 1930.
5. Wilmer, H. B.: Studies in the Treatment of Bronchial Asthma, J. A. M. A. **89:** 956, 1927.
6. Eiman, J.: Studies in the Etiology of Bronchial Asthma, J. A. M. A. **89:** 953, 1927.

1803 PINE STREET.

(For discussion, see page 460.)

SKIN TESTS IN NORMAL INDIVIDUALS WITH MIXTURES OF ATOPEN AND REAGIN*

LOUIS B. BALDWIN, M.D.
ROCHESTER, N. Y.

THE present study was initiated with a view to determining whether or not a mixture of atopic serum with its specific atopen produces a toxic substance which will manifest itself by a positive skin reaction when it is injected into the normal, nonsensitive skin. This question has been previously studied but with a divergence of opinion. While Coca and Grove[1] at first thought that a toxic substance might possibly be formed in this way, later Levine and Coca[2] came to the conclusion that reactions with the mixtures were not larger than those produced with mixtures of serum and physiologic salt solution. In agreement with this latter view, Clarke and Gallagher[3] concluded that atopic reagins did not produce the typical skin reactions when neutralized in the normal skin, and further assumed that the mechanism of the atopic skin reaction must involve reagin, specific atopen, and normal skin cells and that the reagin must act upon the cell before coming in contact with the atopen. More recently, however, from their experiment on thirteen normal individuals, Gay and Chant[4] concluded that injections of mixtures of serum from timothy sensitive individuals with timothy extract did give intradermal reactions larger than any of the control sites. They therefore implied that a reacting substance was produced by such mixtures. This point is obviously of importance, as upon it hinges the question whether in human beings the allergic reaction is or is not dependent upon the formation of an anaphylatoxin-like substance. If such is the case, one might assume that the tissue cells are acted upon by it but do not otherwise participate in the reaction. From my own observations, however, I do not believe this to be so.

The sera of three patients were selected for this experiment. They were hypersensitive to ragweed, timothy, and horse dander, respectively. In each case there was a high concentration of reagins as determined by obtaining passive reactions in normal receptive individuals with high dilutions of the serum. Only freshly drawn serum was used, because of the observation made by Gay that false reactions may occur from serum which has stood in the ice box. The intracutaneous tests were made on eight or ten individuals who were normal and not hypersensitive, and as far as possible corresponding areas were selected on the

*From the Department of Medicine, University of Rochester, School of Medicine and Dentistry.

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two forearms. All the solutions were prepared shortly before the tests were made. They consisted of appropriate mixtures of concentrated extracts of atopen containing between 30 and 40 mg. nitrogen per cent and undiluted serum in the proportion of 1:2. For control purposes combinations were made of the test serum with Coca's solution, of normal serum with Coca's solution, and of normal serum with the atopen giving a positive reaction in the individual from whom the atopic serum was obtained. As an additional control, corresponding mixtures were made of atopic serum with an unrelated atopen; that is to say, one which did not produce a reaction in a site passively sensitized with the atopic serum. For example, when using the serum taken from the ragweed sensitive individual, it was mixed in a proportion of 2:1 with

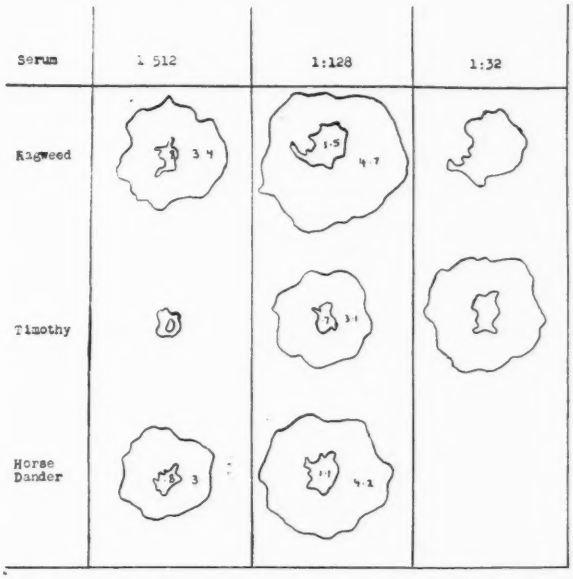

Chart I.—Reactions obtained in passively sensitized skin sites with high dilutions of three sera. Figures represent diameters measured in centimeters.

timothy pollen extract. The various solutions were further diluted ten and one hundred times with normal salt solution before being used for the tests.

Chart I shows the reactions obtained in passively sensitized skin sites with high dilutions of the three sera. As will be noted, the sites sensitized with dilutions of 1:512 of the sera from the ragweed and horse-dander hypersensitive individuals gave definite though mild reactions, while with the serum taken from the timothy hypersensitive case no reaction was obtained with the 1:512 dilution but was obtained with the 1:128 dilution.

Charts II, III, and IV give a graphic picture of the results of this experiment. I do not believe that these findings support the conclusions of Gay and Chant, namely, that mixtures of the serum of hypersensitive

Test Subject
Dilated 1/10 2 Timothy serum 1 Timothy
Dilated 1/100 2 Timothy serum 1 Timothy
Dilated 1/10 2 Timothy serum 1 Ragweed
Dilated 1/100 2 Timothy serum 1 Ragweed
Dilated 1/10 2 Timothy serum 1 Cocas sol
Dilated 1/100 2 Timothy serum 1 Cocas sol
Dilated 1/10 2 Normal serum 1 Cocas sol
Dilated 1/100 2 Normal serum 1 Cocas sol
Dilated 1/10 2 Normal serum 1 Timothy
Dilated 1/100 2 Normal serum 1 Timothy
1
2
3
4
5
6
7
8
9
10

Chart II.—Response of normal skin to mixtures of atopen and reagin which have stood in test tube three hours.

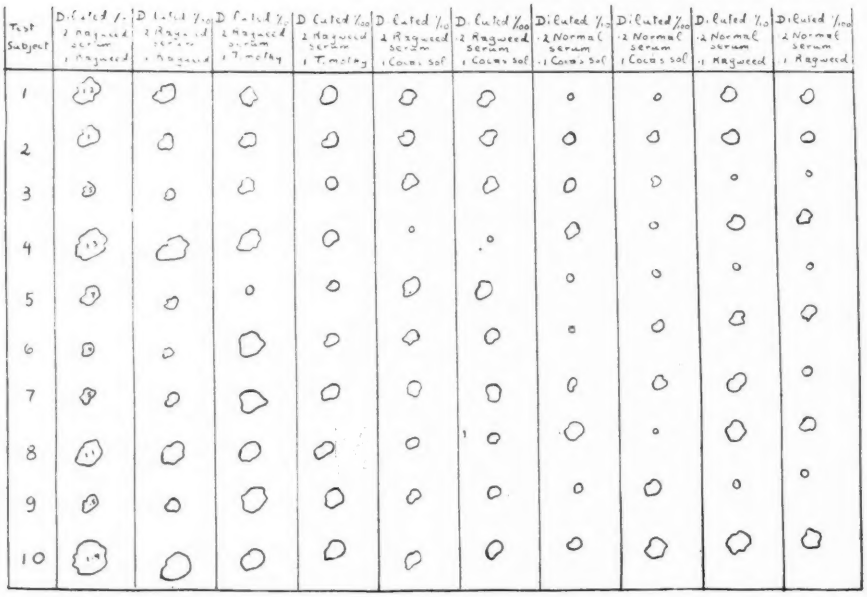
Test Subject
Dilated 1/10 2 Ragweed serum 1 Ragweed
Dilated 1/100 2 Ragweed serum 1 Ragweed
Dilated 1/10 2 Ragweed serum 1 Timothy
Dilated 1/100 2 Ragweed serum 1 Timothy
Dilated 1/10 2 Ragweed serum 1 Cocas sol
Dilated 1/100 2 Ragweed serum 1 Cocas sol
Dilated 1/10 2 Normal serum 1 Cocas sol
Dilated 1/100 2 Normal serum 1 Cocas sol
Dilated 1/10 2 Normal serum 1 Ragweed
Dilated 1/100 2 Normal serum 1 Ragweed
1
2
3
4
5
6
7
8
9
10

Chart III.—Same as Chart II.

individuals with the substances to which they react produce consistently larger reactions than mixtures of such sera with other substances. To be sure, some of the results taken alone might warrant such an assumption, such as, for instance, Nos. 2, 4, and 6 in Chart II; Nos. 1, 4, 8, and 10 in Chart III, and Nos. 1, 5, and 8 in Chart IV. These reactions incidentally were larger than any of the controls. But, on the other hand, there were many instances in which the controls gave as large or larger reactions than the test mixtures, as will be noted by referring to the three charts. Most of the substances were injected three

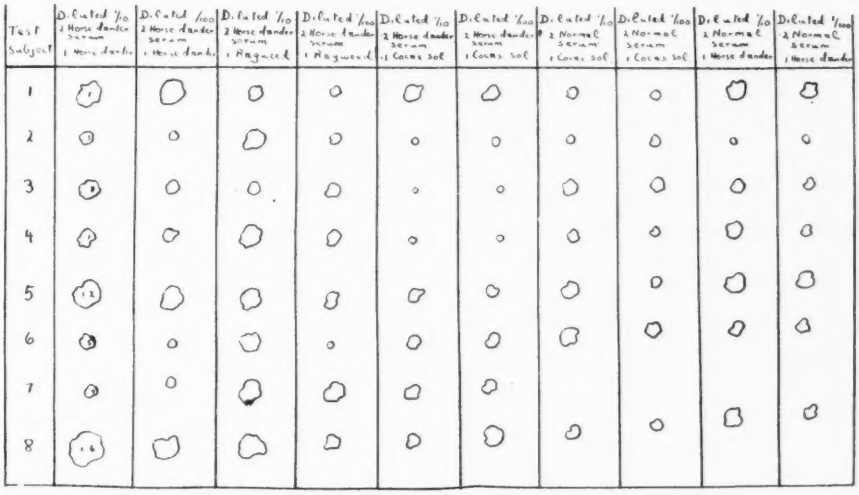
Test Subject
Diluted 1/10 2 Horse dander Serum 1 Horse dander
Diluted 1/100 2 Horse dander Serum 1 Horse dander
Diluted 1/10 2 Horse dander Serum 1 Ragweed
Diluted 1/100 2 Horse dander Serum 1 Ragweed
Diluted 1/10 2 Horse dander Serum 1 Cocas sol
Diluted 1/100 2 Horse dander Serum 1 Cocas sol
Diluted 1/10 2 Normal Serum 1 Cocas sol
Diluted 1/100 2 Normal Serum 1 Cocas sol
Diluted 1/10 2 Normal Serum 1 Horse dander
Diluted 1/100 2 Normal Serum 1 Horse dander
1
2
3
4
5
6
7
8

Chart IV.—Same as Chart II.

hours after the mixtures were made, though in three instances, Nos. 7, 8, 9 in Chart II, they were allowed to stand twenty-four hours at room temperature before carrying out the tests.

From this study, it does not seem as if an anaphylatoxin or analogous substance is formed from mixtures of atopen and reagin in the test tube.

REFERENCES

1. Coca, A. F., and Grove, E.: J. Immunol. **10:** 445, 1925.
2. Levine and Coca, A. F.: J. Immunol. **11:** 411, 1926.
3. Clarke, A., and Gallagher: J. Immunol. **12:** 461, 1926.
4. Gay, L. N., and Chant: Bull. Johns Hopkins Hosp. **11:** 270, 1927.

(*For discussion, see page 464.*)

SENSITIVITY DUE TO CHRISTMAS TREES: A SEASONAL ATOPEN IN BRONCHIAL ASTHMA*

HERBERT MARSHALL COBE, M.D.
PHILADELPHIA, PA.

IN INDIVIDUALS with an allergic background, the causative factor precipitating acute symptoms may be unusual enough to be overlooked. This may be especially so if there are other contributing factors which may be considered responsible for the symptomatology such as the change in barometric pressure, medication, etc. Oftentimes the symptoms of an acute asthmatic attack may be so slightly varied that to the physician there is no change in the usual course while the patient may feel that there is some other contributing cause which makes a slight difference in the usual attack.

The following case reports are interesting in that they show one possible atopen which may be a more generalized factor in a seasonal manifestation of asthma than we have heretofore suspected.

During the Christmas season this past year, the wards of this hospital were decorated in the usual Christmas manner. Holly was hung in the windows and the use of Christmas trees and evergreen was general in the wards and corridors throughout the hospital. A few days before Christmas the trees were put up and trimmed, the trimming consisting of a few glass ornaments and hospital cotton. The species was the same throughout. Shortly after this, all of the asthmatic patients in the women's ward were put together in one of the smaller wards. After two days the patients complained of a "heavy depressed feeling" and a marked tightness across the upper chest "as if a wire band were being tightened." The suffocating feeling was expressed by the patients as "being tighter and different than usual." This peculiarity of symptoms was constant in the three asthmatic patients in the same ward and they gradually increased in severity.

In order to determine the causative agent for this modified type of asthma all of the possible atopens were investigated. The fact that adrenalin was being given at regular intervals with little or no relief brought us to the conclusion that there was some aggravating factor which was prolonging the asthmatic attacks. The adrenalin then being used was substituted by a fresher brand but the effect of change was negligible. The continual bombardment of the mucous membranes by the presence of the atopen was sufficiently strong to overcome any ef-

*From the Wilmer Research Foundation in the Laboratories of the Germantown Hospital, Philadelphia, Pa.

fects of the adrenalin. Later, when the offending atopen was removed, the same adrenalin controlled the attacks.

It was suspected that the decorations might have had something to do with the condition and a series of extracts were made by shaking in a vaccine shaker suspensions of the drying needles, with and without stems from the Christmas tree, the holly leaves, and the holly berries. The extracting solution used was a 12 per cent alcoholic solution. Saline extracts were made the same way: by extracting with normal saline for forty-eight hours. The solutions were then filtered through a Berkefeld filter and checked for sterility. Skin tests were made with the saline suspensions. All tests were done by the intradermal injection of 0.1 c.c. of the extract. A 0.1 c.c. control of normal salt solution was used.

CASE 1.—Patient was able to work until about Christmas in 1928. At that time she had influenza and has been ill since. Has had asthma for past three years which has been worse since the influenza attack. She has sinusitis and nasal trouble.

Physical Examination.—At that time (Nov. 26, 1929), head and neck were negative. The chest was emphysematous, resonant throughout in type and expansion poor. Breath sounds were bronchovesicular throughout, but were suppressed at the bases posteriorly. The heart was normal in size and position, and the myocardium apparently weak. No murmurs were heard. The pulse was poor in force and volume. Blood pressure 130/80. Abdomen and extremities negative.

Skin Reactions.—The major reactors were:

Ragweed giant	5 plus
Ragweed short	5 plus
Sunflower	4 plus
Rose	3 plus

The patient reacted to eleven other proteins with one or two plus reactions.

Desensitization was started with pollen extracts and autogenous vaccines and the patient was discharged from the hospital much improved Nov. 21, 1929.

On Dec. 21, 1929, one month after discharge, the patient was again admitted to the hospital. One week previously her asthma became greatly increased and she was admitted for treatment and study. On Dec. 21, the patient had a severe asthmatic attack. The following day the patient complained of a "different type of asthma" which suggested acute pulmonary edema. She coughed up larger quantities of a frothy mucus than usual.

On Dec. 29 the patient was tested with extracts of Christmas decorations.

Reactions.—

Control	plus-minus
Holly leaves	negative
Holly berries	negative
Christmas tree	5 plus

The reaction following this test was sufficient to bring on an asthmatic attack which had to be controlled by adrenalin. The decorations were removed and on the following day the asthma began to improve, and there were no acute attacks thereafter.

CASE 2.—Patient is an adult white female about forty-five years of age. Admitted to the service of Dr. H. B. Wilmer with a previous diagnosis of bronchial asthma.

Previous History.—Asthmatic attacks began about three years previously following an acute and severe case of bronchitis. Patient is extremely susceptible to colds and her asthma is increased after all acute respiratory infections. She had been admitted to the hospital previously, in the fall of 1928, for this condition. She was studied and treated at the time and discharged much improved. During the past summer she has been practically asthma free. About a week previous to her admission to the hospital this time her asthma was much worse.

Physical Examination.—Head and neck grossly negative. Chest: Dullness to flatness at both apices posteriorly, hyperresonant over the remaining chest on both sides with typical asthmatic respirations and râles. Abdomen and extremities were negative.

X-ray reports showed no pathologic condition of the chest. Allergic skin tests. Major reactors were:

Tuna fish	3 plus
Beets	2 plus

There were a few other reactions of one plus.

Shortly after admission to the ward where Christmas trees were already up, the patient's asthma grew much worse and she complained of a "great tightness high up in the chest." There was the same frothy light sputum that was observed in the first case and the patient remarked that it was not the usual viscid type. Questioning showed that there was a Christmas tree up in the home of the patient just prior to her admission.

The patient was tested with the extracts made from the Christmas decorations and reacted as follows:

Saline control	negative
Holly leaves	negative
Holly berries	plus-minus
Christmas tree	4 plus . . . with marked pseudopods and an area of erythema which extended from the site of inoculation halfway up the forearm.

CASE 3.—This patient was an asthmatic of long standing who had been admitted to the hospital a month before. She had been responding to treatment nicely. On Dec. 29, 1929, she had an acute asthmatic attack and died in a few moments. The postmortem diagnosis of cause of death was: Asthma, partial pulmonary atelectasis and chronic bronchitis. Unfortunately, this patient died before she could be tested with the Christmas tree extracts.

DISCUSSION

Black,[1] cited a case of cedar hay fever. This case was due to the pollen of the cedar tree. In the trees from which the extract we used was made, there was no pollination at this time. The extracted solutions were examined under the microscope before they were run through the Berkefeld filters and no pollen grains could be identified either before or after extraction. There was, however, a very definite desquamation of the epithelium due to drying of the needles, and this was the substance which extracted most easily and thoroughly. Solutions of the drier needles gave the most marked reactions. There may be a slight atopic reaction from the oils contained in the needles and stems but this appeared to extract in later tests to a slight and negligible degree. The sensitivity seems definitely due to the atopic action of the desquamating epithelium of the drying needles. The species of trees used and from which extracts were made was *Picea mariana*.[2]

CONCLUSIONS

Christmas decorations are to be considered as potential seasonal atopens in bronchial asthma.

Perennial attacks of bronchial asthma occurring at the holiday season should be checked for Christmas tree sensitivity.

Specific asthmatic attacks may be precipitated by Christmas trees, black spruce, species: *Picea mariana*.

BIBLIOGRAPHY

1. Black, J. H.: J. ALLERGY 1: 71, 1929.
2. Commonwealth of Pennsylvania, Dept. of Forests.

SOME FINDINGS OF ANTRAL STUDIES WITH IODIZED OIL IN PATIENTS WITH BRONCHIAL ASTHMA*

PHILIP S. STOUT, M.D.
PHILADELPHIA, PA.

THAT the various air cells of the head may have some influence on other parts of the body has been discussed for years and that infected air cells have a profound effect on some of the other parts of the body has been proved beyond question. However, just how much pathologic air cells have to do with bronchial asthma is still under discussion. Some difficulty has been experienced in the past in making an accurate diagnosis of the condition of these cells. It is these with which we are concerned in this paper. A number of methods have been suggested and used to ascertain the conditions present in one or both antra of Highmore.

For some time now roentgen ray opaque substances have been injected, to be followed at once by an x-ray picture. We have injected more than one hundred and fifty antra, including such conditions as bronchial asthma, hay fever, hypertrophic ethmoiditis, atrophic rhinitis, pansinusitis, etc. We have selected fifty cases of bronchial asthma for the present study.

The procedure was to have an x-ray picture of the antra before making the injections and then anteroposterior and lateral x-ray pictures after each injection of one side. These were made about a week apart. When compared to one another, these showed the condition of the antra and also the amount of retention from the preceding injection.

The method used was to cocainize under the inferior turbinate, and then to inject the oil with a Vim syringe with a screw-on needle or a Luer-Lock syringe large enough to hold at least 5 c.c. of the iodized oil or other substances to be used. The needle must be stout enough to be pushed through the nasal antral wall without bending or breaking. These injections, with a little practice, can be made without pain or discomfort. We have injected patients from the ages of five years to sixty-seven years; white, colored, and Chinese; all under local anesthesia. Incidentally, in the very young, it is most difficult to get through the antral wall even when the patient cooperates. The child's

*Read before the Sixth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 3, 1930.

Fig. 1.

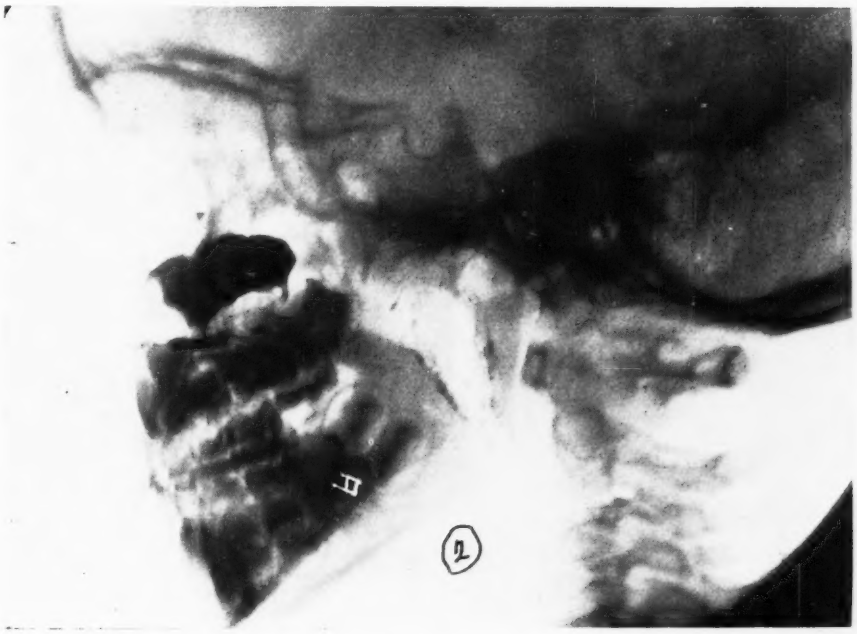

Fig. 2.

Figs. 1 and 2.—Age 5 years. Asthma for three years. Note filling defect. This injection of lipiodol was made with local anesthesia.

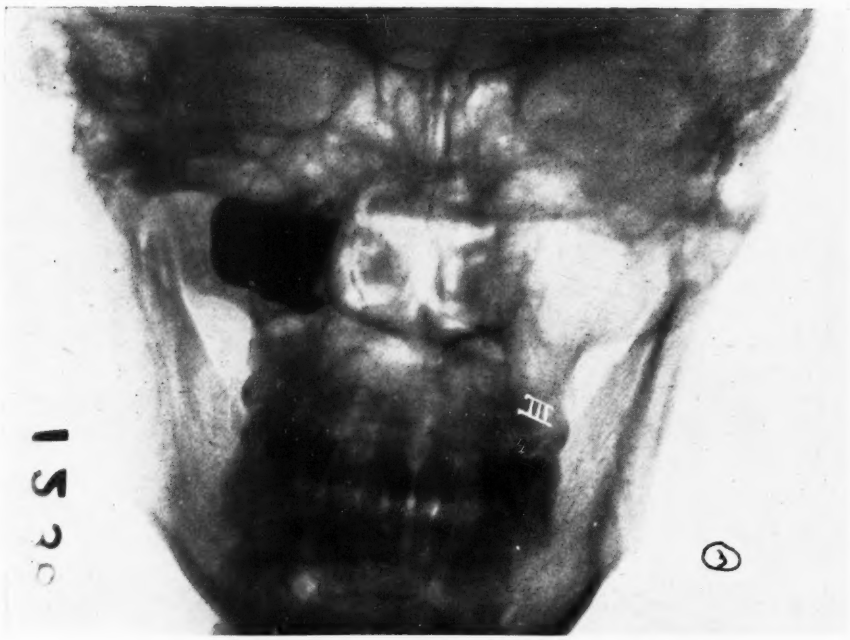

Fig. 3.

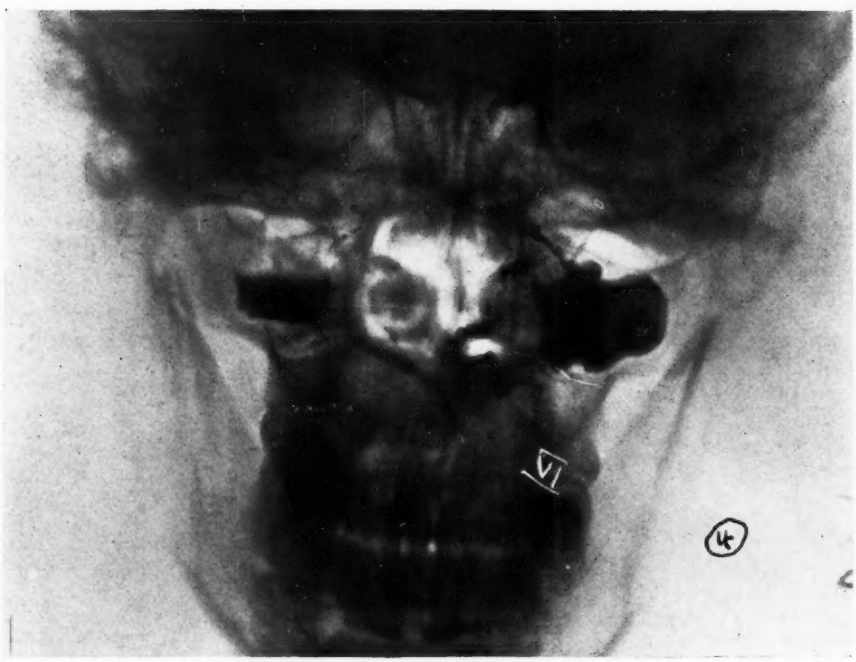

Fig. 4.

Figs. 3 and 4.—Asthma for four weeks. Notice amount of retention in right antrum after one week, also that something is preventing it from coming in contact with the floor of the antrum.

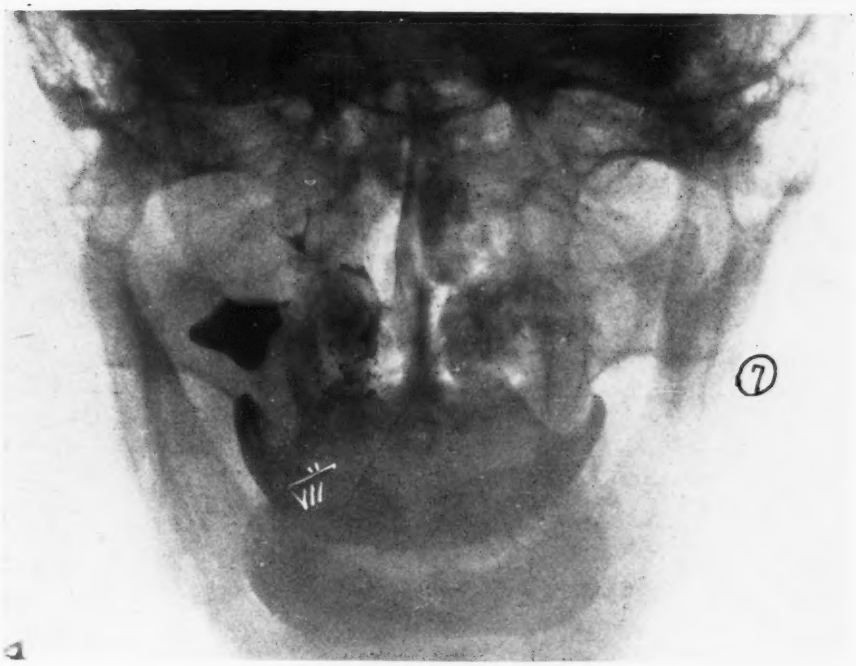

Fig. 5.

Fig. 6.

Figs. 5, 6, 7, and 8.—Asthma for seven years. Lipiodol. Both antra were operated upon. Bony cyst found in each with polyps and thickened mucous membrane.

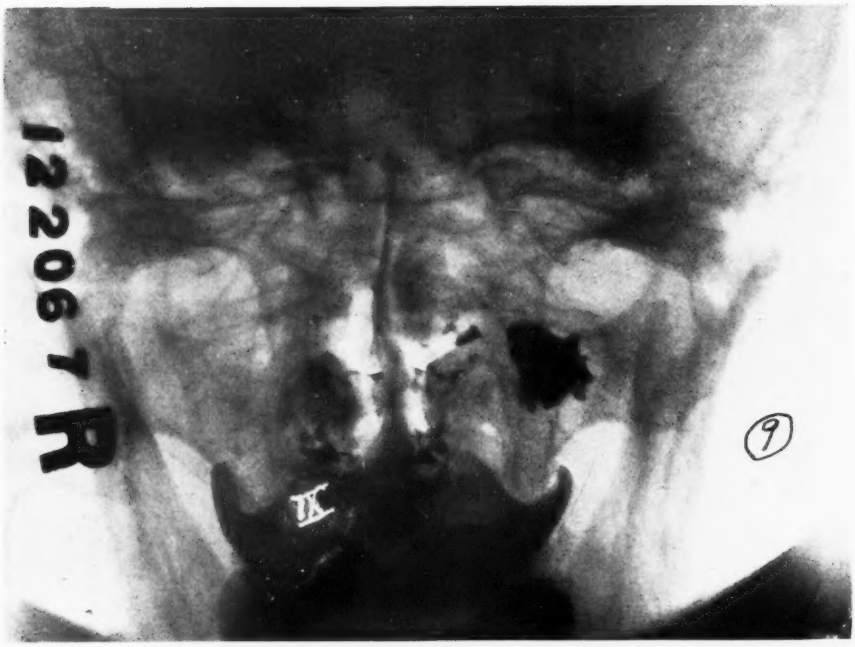

Fig. 7.

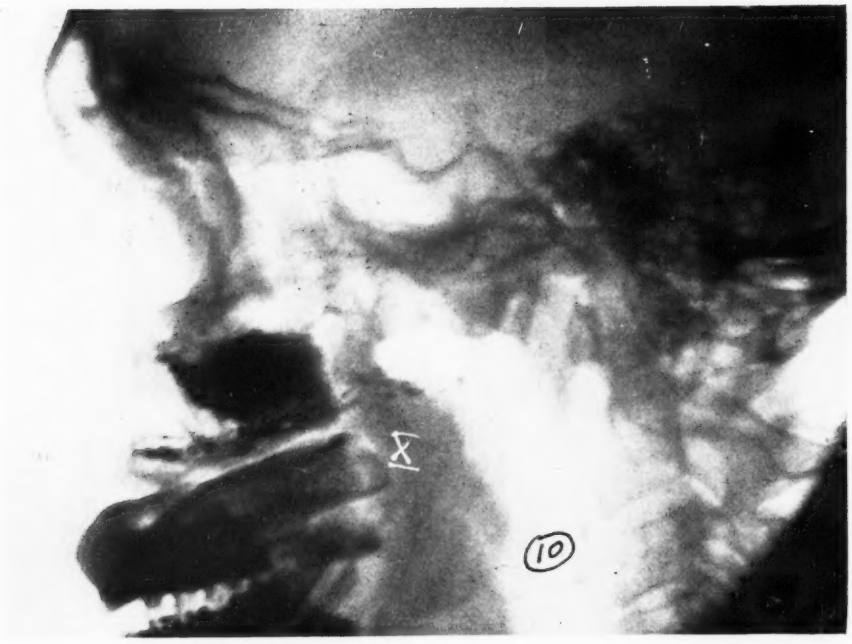

Fig. 8.

antrum does not hold as much as an adult's, but it holds more than one might expect for the age.

There is just a little reaction in some patients, such as pain in the cheek on the side where the injection was made. Pain may radiate down into the cervical glands of the neck and at times there is pain in the area of the thyroid gland. The pain may last four or five days but, other than that, when the injection is properly done, there have been no untoward symptoms.

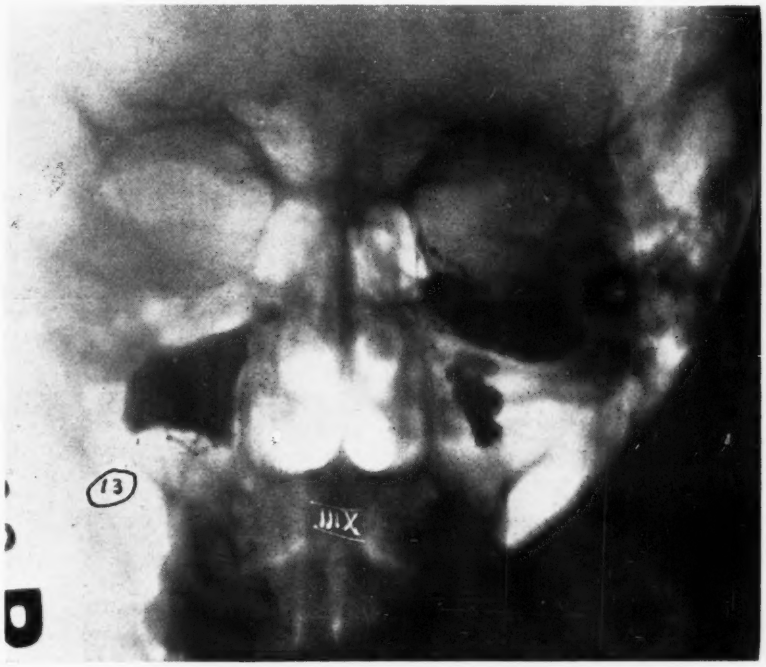

Fig. 9.—Asthma for eight years. The injection entered the soft tissues beneath the eye. This caused considerable redness and swelling of the tissues around the eye but did not affect the sight. A month later an x-ray showed that most of this injection had left the tissues. This occurred once in 150 cases.

The iodized oil shows the size and shape of the antra, the presence or absence of septum, débris, thickened mucous membrane, polyps, bony cysts, and filling defects. It is possible to compare one side with the other, and thus to tell the length of time it takes for the antra to empty. There is often some improvement in the asthmatic condition for a while after the injection. Table I shows the findings in fifty cases of bronchial asthma, with the results of inspection, transillumination, x-ray, and iodized oil injection compared. Table II gives the results obtained with lipiodol and comparison with other methods. Of the fifty patients, seventy-nine antra were injected.

Fig. 10.

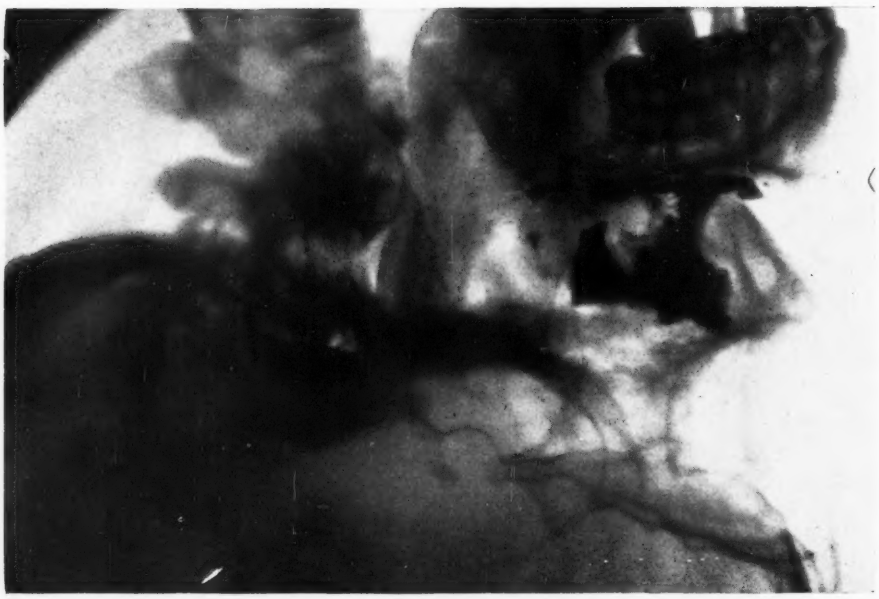

Fig. 11.

Figs. 10 and 11.—Asthma for three years, age 34 years. Note filling defect right and left, left operated upon. Large part of the antrum outside of oil-filled cavity. Polyps in outer cavity.

TABLE I

FINDINGS IN FIFTY CASES OF BRONCHIAL ASTHMA. RESULTS OF INSPECTION, TRANSILLUMINATION, X-RAY, AND IODIZED OIL INJECTION COMPARED

NO.	SEX AND AGE	SIDE	IN-SPEC-TION	TRANS-ILLU-MINA-TION	X-RAY	IO-DIZED OIL	LA-VAGE	SKIN RE-AC-TION	OPERATION
1.	F. 43	R.	P.	+*	+	O.K.	O.K.	+	Bilateral polyps; Thickened M.M.
		L.	P.	+	+	+	+		
2.	F. 67	R.	O.K.		O.K.	O.K.		0	
		L.	O.K.	+	+	+	+		L. Polyps; Thickened M.M.
3.	F. 48	R.	P.	O.K.		+	+	0	
		L.	O.K.	O.K.		+	+		
4.	F. 47	R.	O.K.	O.K.		O.K.		±	
		L.	O.K.	O.K.		O.K.		±	
5.	M. 32	R.	O.K.	O.K.	+	+	O.K.	+	
6.	M. 50	R.	O.K.	O.K.	O.K.	O.K.		+	
		L.	O.K.	O.K.	±	O.K.		−	
7.	M. 61	R.	O.K.	+	±	+	+	+	R. Polyps; Thickened M.M.
8.	F. 46	R.	O.K.	±	±	+	±	0	
9.	M. 41	R.	O.K.	O.K.	+	±		+	
		L.	Ulcer	O.K.	+				
10.	F. 38	R.	O.K.	+	++	+		0	R. Polyps; Thickened M.M.
		L.	O.K.	+	+				
11.	F. 40	R.	O.K.	+	+	+		0	
12.	M. 63	R.	P.	±	+	O.K.	O.K.	0	
		L.	P.	±	O.K.	O.K.	O.K.		
13.	M. 54	R.	P.	±	±	+	+	0	R. {Bony Cyst; Pus; Polyps; Thickened M.M.
		L.	O.K.	±	±	+	+		L. {Bony Cyst; Polyps; Thickened M.M.
14.	F. 57	R.	P.	±	+	+		0	
		L.	P.	±	+	O.K.			
15.	M. 31	R.	P.	±	±	+		+	
		L.	P.	±	±	+			
16.	M. 17	R.	P.	±	+	±	+	+	
		L.	P.	±	+		+		
17.	M. 58	R.	O.K.	+	O.K.	O.K.		+	L. Septum in antra seen with oil injection.
		L.	O.K.	+	O.K.	O.K.			
18.	M. 47	R.	P.	±	+	+		0	
		L.	P.	±	+	±			
19.	F. 52	L.	O.K.	+	±	O.K.		+	
20.	M. 68	R.	O.K.	+	+	+	O.K.	+	
21.	M. 30	R.	O.K.	+	O.K.	O.K.		+	
22.	M. 33	R.	O.K.	O.K.	±	+	O.K.	+	
23.	F. 30	R.	O.K.	O.K.	O.K.	±		+	
		L.	O.K.	O.K.	±	O.K.			
24.	F. 42	R.	O.K.	O.K.	+	±	O.K.	±	
		L.	O.K.	O.K.	O.K.	+			
25.	M. 65	R.	O.K.	+	±	+		+	R. R. Antra Polyps; Bony Cyst.
		L.	O.K.	O.K.	±	+			
26.	F. 37	R.	P.	O.K.	O.K.	O.K.		0	
27.	M. 25	R.	+	+	+	+	±	±	R. Polyps; Thickened M.M.
		L.	+	+	+	+	±		L. Polyps; Thickened M.M.
28.	F. 44	R.	O.K.	O.K.	+	±	+	0	
		L.	O.K.	O.K.	−	±			
29.	M. 38	R.	O.K.	+	O.K.	O.K.		+	
30.	M. 51	R.	O.K.	+	O.K.	+		+	
		L.	O.K.	+	O.K.	+			
31.	M. 38	R.	O.K.	+	O.K.	+		+	R. Polyps; Thickened M.M.
		L.	O.K.	+	±	+			L. Polyps; Thickened M.M.
32.	F. 53	R.	O.K.	+	O.K.	+		+	
		L.	O.K.	+	±	+			

TABLE I—CONT'D

NO.	SEX AND AGE	SIDE	INSPECTION[1]	TRANSILLUMINATION[2]	X-RAY	IODIZED OIL	LAVAGE	SKIN REACTION	OPERATION
33.	M. 12	R.	O.K.	O.K.	O.K.	+		+	
34.	F. 50	R.	O.K.	±	O.K.	O.K.		0	
		L.	O.K.	±	±	O.K.			
35.	M. 48	R.	P.	O.K.		+		0	
		L.	P.	O.K.		+			
36.	M. 6	R.	O.K.	±	+	+		+	
		L.	O.K.	±	+	+			
37.	F. 48	R.	O.K.	±	+	O.K.		±	
		L.	O.K.	±	O.K.	+		−	
38.	F. 58	L.	P.	+	O.K.	+		0	
39.	F. 65	R.	P.	+	±	+		+	
		L.	P.	+	±	+		−	
40.	M. 5	R.	Pus	+	O.K.	+		+	
								−	
41.	M. 42	R.	O.K.	+	O.K.	±		−	
		L.	O.K.	+	±	±			
42.	M. 45	R.	P.	±	+	+		+	
		L.	P.	±	O.K.	+			
43.	M. 53	R.	P.	O.K.	O.K	+		+	
		L.	P.	O.K.	+	+			L. Polyps; Thickened M.M.
44.	F. 39	R.	O.K.	O.K.	+	+		0	
		L.	O.K.	O.K.	+	+			
45.	M. 58	R.	P.	O.K.		+		+	
		L.	P.	O.K.		+			
46.	F. 32	R.	O.K.	±	O.K.	+		+	
		L.	O.K.	±	±	+	O.K.		
47.	F. 51	R.	O.K.	+		+		+	
		L.	O.K.	+		+			
48.	F. 47	R.	O.K.	±	O.K.	O.K.		±	
		L.	O.K.	±	O.K.	±			
49.	M. 58	R.	P.	+	+	+	O.K.	0	R. Polyps; Thickened M.M.
		L.	P.	+	+	+	O.K.		Both Ant.
50.	M. 47	R.	O.K.	O.K.	O.K.	O.K.	O.K		
		L.	O.K.	+	+	+	O.K.	0	

* + = pathology.
† ± = questionable.

TABLE II

RESULTS OBTAINED WITH LIPIODOL COMPARED WITH THOSE OBTAINED BY OTHER METHODS

Lipiodol Injection	DISEASED 50			SUSPICIOUS 9			NORMAL 20		
	D[1]	S[2]	N[3]	D	S	N	D	S	N
Inspection	21	–	29	2	–	7	5		15
Transillumination	20	16	14	2	3	4	6	7	6
Simple X-ray	23	14	10	4	1	4	4	4	10
Lavage	7	3	4	2	–	1	–	–	3
Positive Skin Reactions	28	7	13	2	2	5	7	6	7

[1]D = Diseased.
[2]S = Suspicious.
[3]N = Normal.

SUMMARY

Roentgen-ray opaque substances injected into the antra offer the best method we have found so far for diagnosing chronic diseases of the antra of Highmore.

269 SOUTH NINETEENTH STREET.

(*For discussion, see page 471.*)

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

SIXTH ANNUAL MEETING, ATLANTIC CITY, N. J., MAY 3, 1930

Abstracts of Proceedings

Observations on the Mechanism of Wheal Formation. H. L. ALEXANDER, ST. LOUIS, MISSOURI. (To be published in a later issue.)

A Biologic Classification of Food Allergens for Group Testing. DR. WARREN T. VAUGHAN, RICHMOND, VA. (For original article, see page 385.)

DISCUSSION

DR. JOHN A. MURPHY, PHILADELPHIA.—I think Dr. Vaughan is to be congratulated on presenting this paper to us and doing a bit of fundamental work in trying to aid us in picking out and orienting some of our problems in testing with foods. We have all been impressed, I think, with the fact that food testing has frequently been a little difficult to coordinate with the symptomatology. I have been using the same group that Dr. Vaughan has, and while I have not gone into the matter with as much care as he has, I am impressed up to the present time with the fact that I am picking out definitely some positive reactions to foods which heretofore I have been missing.

I thought that perhaps I was getting some false positives in contradistinction to false negatives, and recently through the courtesy of Dr. Russ of the Mulford Company I have dialized some of these group extracts with the idea of removing possible irritative factors. My work has not gone very far with this, but at the present time those patients in whom I have secured a positive reaction to the legume group, on retesting with the dialized legume extract they gave the same type and same character of group reaction as they did in the first place.

I am not prepared to say whether dializing is going to help these particular extracts or not. However, I do believe that the use of these extracts is going to aid us considerably in our problem of working out a management for allergic cases that are sensitive to foods.

DR. AARON BROWN, NEW YORK.—I would like to ask Dr. Vaughan, in view of the negative reactions with cabbage in the patient having symptoms of indigestion, whether he was able to correlate whether cabbage caused any disturbance, that is, indigestion, if it were cooked, or if it were raw—whether these cooked and raw foods have any bearing on this, when the group reactions are negative.

DR. S. S. LEOPOLD, PHILADELPHIA.—I want to ask Dr. Vaughan whether any work has been done in correlating the food reactions with pollen reactions. Clinically, one is sometimes impressed by the fact that certain people who are pollen-sensitive have certain positive food reactions, and I wonder whether there is any botanical explanation for that.

DR. PHILIP LEVINE, BROOKLYN.—Within a certain group I notice from Dr. Vaughan's charts that positive reactions in many cases were obtained from some, but not from all. I would like to raise the point whether there is something about the extracts of these foodstuffs which accounts for the difference; that is, if the substance is of such nature that one has to modify the procedure of extracts somehow in order to make them fit in with the classification.

DR. WARREN T. VAUGHAN.—I can answer the last question first, and with it Dr. Murphy's discussion. Of course, there is a possibility of variation in the extracts. I cannot give you any definite information on that. I recall that one of the chemical companies had considerable difficulty in getting a tuna fish extract that would not give a false positive reaction. My discussion of the false positive reactions I have left out because they appear in my paper, and I wanted to save time. I am sure there are some false positive reactions, particularly among the melon family, and the compositae, the banana and ginger. I am rather inclined to believe that the reason for a false positive is a little different from what Dr. Murphy suggested. According to the material that Dr. Russ of Mulford Laboratories made up, each of the extracts contains 500 protein units per c.c., and I have asked him to make the groups up so that the group would contain 500 of each of the members, so there are many more protein units in some of the groups than in others. The plan is to check that, and I have done this to a slight extent, but not enough to be sure of the terms yet with reference to other groups in which the total number of protein units of the mixture is no greater than the number of protein units for each of the individuals, namely 500. Also I have a plan—and this I have not started yet—of using as an additional control a group in which there is no biologic relationship at all; just to pick them from unrelated proteins, and proteins which from experience usually give negative reactions, so that they will serve as an additional control. Banana and ginger give, I believe, false positives. They are only two allergens which represent 1,000 units; some of the others have up to 3,500 units and yet do not give as frequent positives.

Dr. Brown's suggestion, I think, is very important—the possibility of there being a chemical change resultant on cooking, and whether cabbage when not cooked will give symptoms, and when cooked will not give symptoms. With regard to cabbage, in that individual case, I do not know. I mentioned the cooking of pear in another case. Uncooked pear would cause allergic manifestations; cooked pear would not.

As to Dr. Leopold's remarks of the possibility of cross reaction between foods and pollens, I have only a few cases in which I have seen that. As a rule, we have not seen it. For instance, take the members of the legume family. Those sensitive to legumes are not sensitive to clover and alfalfa to any extent in those cases which we tested. I have followed that up, but have not obtained anything definite yet. I have some patients, especially three very interesting cases sensitive to wheat or corn pollen; when they eat wheat or corn meal, they develop hay fever symptoms. The possibility of a clover cross reaction I have already mentioned.

Of course, we must remember that in some of these families we are dealing with tremendous numbers. Among the different groups that we have discussed there are often hundreds of species. There are 1,000 to 10,000 species in the compositae. We would therefore expect to get more frequent cross reactions among some than others. Briefly, our chief evidence of cross reaction is among such groups as the legumes, the peach-plum family, the drupaceae, and the melon family, and the family represented by parsnip, celery, parsley, and carrot, and finally the liliaceae, garlic, onion, and asparagus.

Ragweed Dermatitis. OTELIA BENGTSSON, M.D., OSSINING, NEW YORK.

In testing 25 known ragweed cases with the oil fraction of the ragweed pollen Dr. Chobot found about 4 cases of resulting dermatitis. Thirty-five patients who were not sensitive to ragweed were tested with:

1. Ragweed by scratch-patch test.
2. One per cent alcoholic suspension of the oil intradermally.
3. Ragweed pollen extract 0.01 mg. N per c.c.
4. Alcoholic extract of ragweed leaf.

Patches were left on one week, and observations were made for at least three weeks. Eighteen cases were completely negative; 8 gave a one plus reaction; that is, a small itching papule appeared at the site of the intradermal suspension after about ten days; 5 gave a reaction at both the scratch and the intradermal sites. Three gave a dermatitis starting in ten days, two weeks, and three weeks after the primary tests. The dermatitis started with a small papular or papulovesicular lesion, such as the one-plus reaction at the site of the intradermal alcoholic suspension injection. A few days later the scratch site appeared and the dermatitis then spread over an area several inches in diameter; it had a coppery red base with many vesicles and a very marked itch. The dermatitis reached its height in three weeks and then began to subside. A fourth case developed an early dermatitis which was due to the adhesive plaster. On testing with the various ingredients of the plaster the patient was found to be sensitive to rosin.

DISCUSSION

DR. W. W. DUKE, KANSAS CITY.—I should like to mention something simulating ragweed dermatitis; that is, a rash on the face that occurs during the hot weather, being caused by sensitiveness of the skin to heat. I had a patient who had been tested by a number of physicians and the diagnosis was pollen dermatitis of the face. The history was very characteristic. The patient came to me in the middle of winter and this rash on the face was produced in all its glory by heating the skin of the arm. It could be quickly relieved by putting the opposite arm in cold water. This was a heat dermatitis of the face caused by sensitiveness to heat. I bring this up because of the essayist's remark that a rash appeared under an application of adhesive tape. I can easily imagine that adhesive tape applied to the skin, in a person who had skin sensitiveness to local heat, could cause a rash by keeping the skin too warm in that particular area.

Quantitative Skin Tests With Bacterins Prepared From the B. Coli Group. L. W. FAMULENER, M.D., AND JOHN STAIGE DAVIS, JR., M.D., NEW YORK.

In studies on skin reactions following intradermal injections of vaccines (bacterins) prepared from intestinal bacteria, it was often found that the quantitative results appeared to be influenced by various factors. These factors may be roughly grouped as those of (1) physical

nature; (2) biochemical character, and (3) those inherent in the individual, to which may be added recognizable disease conditions in certain instances. Therefore, when such tests are to be applied to determine the presence or absence of skin hypersensibility of the individual to the substance or products of an organism, it is essential that the known factors be taken into consideration in making a final estimate of the result, and in particular, when attempting to assign the degree of skin hypersensitiveness in positive cases.

Among the physical factors influencing the reaction the anatomic structure of the particular area of the skin receiving the injection must be considered. It may be assumed that increased richness of the local lymphatic network of the area would permit an earlier and greater distribution of the injected material, and, in the hypersensitive individual, result in a more marked reaction. Also the mechanical movements of underlying structures may contribute toward the same end. The texture of the skin apparently influences the reaction to a certain extent, as often the reactions appear more intense in the soft, moist type than in the dry, firm integument. The relatively greater quantitative reactions which occur in the upper cubital surface (brachial fossa) of the forearm may, in part, be explained on the basis of the above-mentioned factors. But in general, when the physical factors are equal, the injection of the same vaccine (bacterin) in the same volume and dosage in different skin areas of the body in the same individual caused no marked difference in reaction. The inflammatory reaction following the introduction of the materials may be of such a nature as to offer a physical barrier, through cellular infiltration, which partially walls off and prevents a diffusion of the substance. Other physical factors probably complicate the reaction.

Among the biochemical factors entering into a skin reaction may be included those substances or components of the bacterial cell which may be considered primarily toxic to the cells of the skin, and those substances (split products) arising secondarily from the introduced bacterins through the assumed action of specific antibodies present, either in the tissue fluids, or in the tissue cells. As a working hypothesis to explain certain phenomena which occur, it may be assumed that at least three possible conditions might exist, resulting as follows:

1. No reaction, other than a physical irritation to the introduced bacterial substance, due to absence of specific reacting antibodies in the tissue fluids and in the adjacent tissue cells, leading to negative results.

2. No reaction induced by the bacterins due to neutralizing antibodies in the tissue fluids, or to a state of desensitization of cells, otherwise capable of reacting.

3. A state of sensitivity of the tissue cells without the presence of antibodies in the surrounding tissue fluids, or in insufficient amounts to inhibit completely an interaction of the complex; this results in

variable degrees of an inflammatory process, giving rise to positive skin reactions. Obviously these factors play the leading rôle in the quantitative skin reaction.

Most individuals when subjected to the intradermal test with bacterins prepared from the B. coli group isolated from the intestinal tract of man show a positive reaction. In a series of over one hundred individual cases, we have observed only one exception to this rule. Probably the positive skin reaction with the B. coli bacterin is a manifestation of a defensive mechanism on the part of the body in general. It is possible that a slightly active immunity may be acquired spontaneously, as we have observed that in some instances an individual showed greater reactions to heterogeneous B. coli bacterins than to the autogenous when quantitative tests were done. Finally, we must recognize certain individuals who do not give positive skin reactions themselves, but by whom such a reaction may be passively induced in a second individual's skin by introducing their serum and the specific bacterin. The biochemical reactions entering the "skin reaction" probably are not as simple as assumed—future chemical investigation may invalidate the hypothesis.

Another group of factors influencing the skin reaction would appear to be more or less inherent in the individual. The blonde appears to give quantitatively greater reactions to B. coli bacterins than the brunette type. Age also appears to be a factor, although our group of cases including both young children and aged patients is quite limited. The quantitative tests, however, would indicate that young children gave relatively the least reaction; the aged, the next in order, while the most intense reactions were in a large group, between fourteen and thirty years of age. Normal adults used as controls in the study gave equally marked reactions to heterogeneous bacterins (B. coli) as many of those who were suffering from various disease conditions. Patients who gave a history of digestive upsets appeared to react more strongly than others; those suffering from chronic degenerative diseases did not react more markedly than others in our experience.

It is evident that the occurrence of positive skin reactions following the intradermal injection of bacterins prepared from the colon bacillus are variable, presumably depending upon the interaction of numerous factors which may be present. The degree of reaction simply indicates the balance existing between the variously acting factors.

DISCUSSION

DR. STERLING, PHILADELPHIA.—I would like to know whether the bacterial counts in proportion to the minimums of fluids injected have anything to do with the final results in these reactions.

DR. FAMULENER.—In regard to bacterial counts, we dropped that method a good many years ago. We prepare our vaccines by throwing down the substance in as condensed a condition as possible and make a 1 per cent suspension. From

this 1 per cent suspension which is killed, we take our standard unit and we have found by experience that about 0.01 c.c. of the 1 per cent suspension is the proper amount to use.

Sudden Death From Bronchial Asthma. JOHN A. MURPHY AND E. A. CASE, PHILADELPHIA. (For original article see page 434.)

DISCUSSION

DR. A. H. W. CAULFEILD, TORONTO.—I am getting up only to ask whether there is anyone else who has been as remiss as myself. This Society, I believe, is responsible for careful collection of deaths from asthma, and there are very few collected, as you all know. Within the last two years I have seen four deaths, which is a large number, and I should have reported them, but only on two was a post-mortem examination carefully made by a competent pathologist. Seeing four deaths in two years made me wonder, as I heard this report, if some of us are omitting to mention these deaths, because we have not been in position to work them up as fully as possible.

In the two I obtained, the appearances of the lungs were totally different. There was no particular evidence that these patients died of bronchial asthma, except that in one there seemed to be an acute and absolutely diffuse emphysema of a character that I had never seen before. A microscopic slide showed that all the bronchioles were enlarged, and there was emphysema. Every alveolus was about five times the size it should be. The lung seemed extraordinary in that it was absolutely even over its entire surface.

I only wonder if there are others as remiss as I have been, and if there are more patients dying from bronchial asthma than we think.

DR. S. S. LEOPOLD, PHILADELPHIA.—I want to ask Dr. Murphy whether the coronary arteries were examined in his patient, because there is a clinical history that suggests the possibility of angina pectoris. There is a recent paper by Levine, of Boston, on the use of adrenlin in doses of one c.c. to differentiate between angina pectoris and pseudo-angina. It raises the question whether this patient may have had coronary disease which might have contributed to death and whether this was induced by the doses of the adrenlin used in spite of the fact that this patient is relatively young for a development of angina pectoris under normal conditions.

DR. FRANCIS M. RACKEMANN, BOSTON.—I have seen two other deaths from asthma, and in connection with them I would like to comment on what Dr. Murphy has mentioned. He said the findings showed emphysema with obstruction of the bronchi by a thick substance. That is precisely what our two cases showed, except in them the exudate was quite marked, and could be pulled out with forceps to reveal quite a definite structure. The appearance was so striking that it certainly suggested in our cases that death was due to asphyxia, depending upon the mechanical obstruction by this exudate.

DR. J. A. CLARKE, PHILADELPHIA.—I should like to ask Dr. Murphy whether there were any adhesions between the lung and the pleura or the pericardium. In going over these cases in the literature a large number of them have had rather extensive adhesions between the pleura and in the pericardium. In one patient who died during an attack, we found a complete obliteration of both the pleura and pericardia. There was no cardiac enlargement except on the right side of the heart.

Dr. Murphy's finding of molds in the sputum recalls a very interesting case of death from asthma which we had this last year. A woman ran a considerable temperature for which we could find no reason either during her life or at post-

mortem, except what the pathologist found and believed were multiple abscesses of the right upper lobe. We thought that it was a case of infection, and that was all there was to it. When the microscopic sections came through, we found the so-called abscesses were localized masses of some fungus. It was too late then, of course, to try to grow these fungi but it is interesting to know that Dr. Murphy in his case found the fungi in the sputum.

DR. PHILIP S. STOUT, PHILADELPHIA.—I was interested from the viewpoint of a laryngologist. This patient had ethmoiditis, polyps, and dark antra. I would like to know whether anything had been done to relieve this condition at this time.

DR. MURPHY.—That was our object for getting her into the hospital but her death defeated the purpose.

DR. FERNAND VISTZREICH, NEW YORK CITY.—I should like to hear Dr. Murphy's opinion of this: The patient complained of a definite choking sensation around her larynx. This suggests to me that maybe that was caused by laryngeal obstruction, and the asphyxia might have been secondary to acute laryngeal edema or laryngeal spasm. I wonder if there was any evidence in the postmortem of such a laryngeal condition or any evidence in the history of previous serious laryngeal obstructions.

DR. WARREN T. VAUGHAN, RICHMOND.—Dr. Caulfeild raised a question which no one else has answered. One hesitates to report incompletely worked up material. In the last ten years I have seen two cases of sudden death from asthma. One of them had not been worked up at all. I saw her but twice. Once was during her fatal attack. It appeared to be death from an acute attack of asthma. The second case has been very thoroughly worked up. Death was again apparently due to nothing but an acute attack of asthma. The family refused permission to do an autopsy. I was also wondering in regard to the sense of constriction around the neck, whether it was due to spasm of the accessory muscles of respiration.

DR. W. W. DUKE, KANSAS CITY.—There is something that patients die of that is not related to bronchial spasm or lack of oxygen. I had one patient die suddenly of asthma who did not have very much asthma at the time of death. Something else happened to that patient. I have had several others who almost died.

In this connection, I would like to say that it is very difficult to tell when an asthma patient is dead. I know only one way: that is when the patient becomes cyanosed and the cyanosis disappears. I got that idea from Dr. J. D. Dyke, who called me once about a patient who had been given a pollen injection and reacted violently, with complete stoppage of respiration and intense cyanosis. I told him to keep on working with adrenalin and artificial respiration, which he did, and after a time the patient came back to life, and was as healthy as ever. Dr. Dyke told me he knew the patient was not dead in spite of what he said to me, because the patient was still cyanosed. A dead person is pale. A patient dying of asthma is dying of asphyxia. I think this observation of Dr. Dyke is extremely important and his prolonged efforts in trying to restore life only convinces me that a person dying of asthma should not be given up until he is pale—not cyanosed.

DR. ALEXANDER, ST. LOUIS.—I am very much impressed by the remark of Dr. Leopold that his patient had certainly the symptoms of angina pectoris. Levine and his associates showed that an attack of angina pectoris was induced, as I recall, in eleven out of twelve cases, by one c.c. of adrenalin.

One exception I take to Dr. Leopold's remarks is that an examination of the coronary arteries may show them to be normal.

In this instance the lung weighed only 360 grams which is competent to carry on life. People with emphysema do not die suddenly of acute asphyxia. The asphyxia

that takes place lasts for days, the respiration becomes more and more shallow so that it takes a considerable time for people with emphysema to die. Such cases do not snap out like this one did.

DR. JOHN A. MURPHY.—In reference to Dr. Clarke's comment about the molds, nothing was done with this particular patient. However, the subject of molds has been occupying a corner in my mind for some months, and as a result I have recently tested a few patients with asthma who were showing a reaction to dust at least, with an extract of molds. So far I have nothing to report, but I do believe that molds will come into their own some time or other in our study of this condition.

Dr. Caulfeild, of course, was begging for us to get into the literature with our reports of deaths from asthma, and I think that regardless of whether they are studied up properly with autopsy reports or not, they certainly ought to be reported. We are going along on a rather smooth sea in believing that deaths from asthma are comparatively rare, and may be if we all come out of the woods, we will find that the number is sufficiently alarming to make us a little more aware of the possibility of death in these cases, and not be so sanguine in our conversation with members of the family.

Dr. Rackemann's remarks about his cases resemble mine. In reviewing the literature I find that the pathologic picture seems to differ somewhat. And that, of course, brings up the question of whether or not deaths occur from an uncomplicated asthma. This case we felt was certainly one of uncomplicated asthma.

To answer Dr. Leopold's question about the heart, and I think Dr. Clarke wanted to know about adhesions, there were no adhesions either in the pleural sacs or in the pericardium. The only adhesion that was found was from a postoperative abdominal operation. Concerning the heart itself, I did not read the report of that here because it was normal as far as pathology was concerned. The coronary arteries showed just a slight yellowish tinge, but no patches, suggestive, perhaps, that there might have been a slight degree of beginning degeneration.

As to the larynx and the trachea there was absolutely no evidence of obstruction or edema or other pathologic condition in either.

As to the question of the suddenness of the death in this case, perhaps I was wrong in giving it the title of "Sudden Death from Asthma." I reported it because I saw the patient an hour before her death, when she was sitting up in the chair reading in a comparatively normal state. I am using the element of time there alone.

Dr. Duke was the gentleman who brought out something that I was hoping the rest of you might help me with; that is, what can we do in these crises that occur in asthmatic patients? When they get into that state, one feels rather helpless, as adrenalin sometimes fails to do its work as it ought to and one becomes a little afraid of the constant introduction of it. I feel that the constant use of adrenalin, which would apply to Dr. Alexander's comment, must certainly produce some sort of an angio-spasm, or a condition in the blood vessels that might contribute under those circumstances to the death of the patient.

Active Immunization Against Typhoid Fever With Particular Reference to an Intradermal Method. LOUIS TUFT, M.D., PHILADELPHIA.

In order to investigate the importance of the skin in relation to processes of immunity and particularly to antibody formation, experiments were carried out in both human beings and animals, comparing the antibody response after intradermal, subcutaneous, and intramuscular injections of mixed typhoid vaccine. These investigations dis-

closed the following facts: (1) That small doses of a potent mixed typhoid vaccine given by the intradermal method gave an equal or better response than larger doses by other methods and with comparatively less general and local reaction; (2) that the antigenic power of the vaccine decreased with the aging of the vaccine, and (3) that different strains had varying potency.

On the basis of these findings the author suggests the following as constituting a satisfactory method of active immunization against typhoid: the use of a fresh mixed typhoid vaccine of known potency composed of one billion typhoid and five million each of Paratyphoid A and B, per c.c., given by the intradermal method in doses of 0.05, 0.1, 0.15, and 0.2 c.c., at weekly intervals.

DISCUSSION

DR. PHILIP LEVINE, NEW YORK.—I recall reading a paper recently in which guinea pigs were sensitized with the same dose of antigen, subcutaneously and intradermally. It was found that the guinea pigs which were sensitized intradermally were the more sensitive to anaphylactic reaction. There is also a possibility, aside from the mere point of difference, that there may also be a qualitative difference from the effect of the intradermal as compared to the other methods of injection. I believe this is indicated by some recent studies by Julianelle on intradermal inoculation with pneumococci.

DR. JOHN A. MURPHY, PHILADELPHIA.—It seems to me that Dr. Tuft's work might apply to allergic conditions. We are accustomed to using the skin as the shock organ, and for demonstrating sensitivity to the various allergens, and we know that the skin and the mucous membrane are closely allied in their development. I have been impressed a little with the observation in testing certain so-called non-sensitive cases of asthma with the respiratory bacteria, using the intradermal method, that I am introducing into the skin numbers of bacteria considerably in excess of the probable first dose that we might give of either an autogenous or stock vaccine in treatment. These patients sometimes have a focal reaction as the result of the test, and then have a period of temporary improvement. I have often wondered whether we might not do more satisfactory work if we administer allergens, either in the form of vaccine or pollen extract, or epidermal extract, by intracutaneous injection rather than by a subcutaneous method.

DR. STERLING, PHILADELPHIA.—Several years ago I checked up several cases of pollen desensitization and I found those patients who received desensitization by the intradermal route were much better desensitized and needed much smaller doses than those desensitized by other methods. For the last few years I have given practically all desensitization injections by the intradermal route instead of subcutaneously. The only objection is that occasionally explosive reactions occur with the addition of even a very, very small increase over the preceding dose. I remember one patient last year who about fifteen minutes after the injection went into complete anaphylactic shock with tremendously marked edema and acute swelling of the glottis. She was unable to go home for about two hours, and she was sick for a week after that with a generalized erythema.

DR. BROWN, PHOENIX, ARIZ.—I think Dr. Tuft's suggestion about the age of the vaccine method need not alarm us at all, because the public health service did work ten or twelve years ago on the standardization of these vaccines, by both the intravenous and subcutaneous route, by animal route. Their control vaccine is any-

where from six to twelve months old when it is applied. I think from the clinical angle of immunization of individuals it need give you no concern.

DR. LOUIS TUFT.—I stated at the outset that this was only part of a program of investigation of the intradermal method. I might mention in this connection the results of some work we have done in a preliminary way with Schick-positive individuals. I had occasion to test some individuals who were Schick positive and who have also had a very small dose of toxoid given intradermally as a skin test. We retested that group of about fifty some six weeks or two months after they had been given the toxoid. I did it because I thought there might be sufficient toxoid, if given intradermally, to produce a Schick negative reaction test. To my surprise, in about 15 or 20 per cent of the individuals a very small dose of toxoid given intradermally was sufficient, because of apparently a Schick negative test. This again illustrates the importance of the skin in relation to processes of immunity.

Skin Tests in Normal Individuals With Mixtures of Atopen and Reagin. L. B. BALDWIN, ROCHESTER, N. Y. (For original article, see page 438.)

DISCUSSION

DR. MATTHEW WALZER, BROOKLYN.—This paper is right in line with the work which is going to be presented in the next paper by Miss Bowman. Our results confirm Dr. Baldwin's entirely. There are several factors, however, in this work which must always be remembered in performing these tests. The first is that a neutralized mixture and an unneutralized mixture do not give the same results. Now, you will remember in work which was reported some time ago in our studies on protein absorption, it was found that if one eats the offending atopen, say egg white, and then inserts into the skin a small amount of the serum sensitive to egg white, he will get a slightly positive reaction. This reaction is smaller than the reaction which would occur if the process were reversed; it is a definite reaction with redness, wheal, and itch, but it comes on later. Now, the reason we believe it comes on later is because it takes a certain amount of time for the reagin to get by the atopen, or the egg, in the circulation and become established in the cells.

Likewise in these tests, in working with an unneutralized mixture, one will find that if he waits long enough, he will get a positive reaction which will grow stronger. It will come on slower than the others, but it is definitely positive, and for that reason he is liable to get different results. It takes a long time for pollen atopen to neutralize pollen reagin. It takes a much longer time when one is working with pollen than with horse dander, or any of the danders. As a matter of fact, it took us about five or six hours to neutralize the pollen completely in the test tube.

DR. L. B. BALDWIN.—I tested for the neutralization of reagin in the mixtures in a few instances. In those cases the solutions were neutral.

A Test Tube Neutralization Method for Studying the Identity and Properties of Reagins. MATTHEW WALZER, M.D., AND KATHERINE BOWMAN, NEW YORK CITY.

The identity of any two closely related atopens has hitherto been studied by determining whether neutralization of passively sensitized sites by repeated intradermal tests with each atopen completely desensitizes these sites to the other. (Coca and Grove.) The present

method of study is a modification of the above procedure, taking advantage of the ability of atopens to neutralize the skin-sensitizing power of their specifically related reagins when mixed with them in the test tube. (Coca and Levine.) This eliminates the neutralization or desensitization process in the skin and the difficulties associated with it.

The technic is as follows: A serum known to contain reagins for the atopens in question is mixed in the test tube with a previously determined amount of one of the atopens. The mixture is incubated from one to four hours, depending on the nature of the atopen. Two sites on the skins of receptive subjects are then sensitized with this mixture. After waiting seventy-two hours to allow tissue refractoriness caused by the wheal of the sensitizing injection to subside, one site is tested with the neutralizing atopen to confirm the completeness of neutralization in the test tube. The second site is tested with the other atopen, whose properties are being compared with those of the first. A positive reaction indicates that the two atopens are not identical.

This method is being applied to studies of the antigenic relationship of various members of closely related groups of atopens; for example, the epithelia of horse (Equus caballus), donkey (Equus asinus), and zebra (Equus zebra), the three genera of the family Equidae. Studies with the first serum used show that:

1. Donkey epithelium completely neutralizes the reagins in that serum for horse and zebra epithelium.
2. Horse epithelium completely neutralizes the reagins in that serum for zebra but not for donkey epithelium.
3. Zebra epithelium does not completely neutralize the reagins in that serum for either horse or donkey epithelium.

These results are identical with those obtained with the same serum employing the "in vivo" neutralization method of Coca and Grove. Further studies of this group are being made with other sera. Other groups of atopens are being investigated in a similar manner.

The test tube neutralization method is advantageous for the following reasons:

1. The method is less time-consuming than the "in vivo" method.
2. Results with the test tube method are more reliable, as the element of skin refractoriness persisting on a site after wheals have formed is almost entirely eliminated.

DISCUSSION

DR. PHILIP LEVINE, NEW YORK.—From a biologic point of view, the experiments of Miss Bowman and Dr. Walzer are interesting, although they did not decide conclusively as to the danders of donkey, horse, and zebra. The attempts are interesting as experiments on other than danders of horse and donkey. For instance, when serums of horse and donkey are compared, it is almost impossible to distinguish the two. When, however, red blood cells of the donkey and horse are compared by means of the serum, it is readily possible to differentiate between them. It may be that the difference in the two cases, that of the serum and the red blood

cells, is due to the chemical nature of the substance and the serum proteins involved, and the red blood cells are not protein substances involved.

One might speculate as to what will be developed from the results of the experiments by Dr. Walzer and Miss Bowman if one assumes that the active substance in the danders and protein might perhaps be identical. That, however, does not seem to be so, as horse and donkey danders seem to neutralize each other, and they both seem to be different from that of the zebra. Certainly, the technic employed by them in testing the patient is a very superior method.

Deformity of the Face Caused by Nasal Allergy in Childhood. W. W. DUKE, M.D., KANSAS CITY.

It may be assumed that for the normal development of the paranasal sinuses, the sinus membranes must be in good order and the

Fig. 1.

openings from the nose into these sinuses must be patent, at least for the greater portion of the time. If the sinuses should be filled with mucus over prolonged periods of time, and if the membranes should be edematous and polypoid, and if the openings should be closed by edema and mucus, we should expect a pathologic condition in the development of the sinuses. The fact is that if we look for it we can usually find some pathologic condition in the physiognomy of allergic children which is traceable to maldevelopment in the region of the paranasal sinuses. This deformity can be observed even though nasal allergy may be so slight as not to attract grossly the attention of the physician or even the attention of the parents of the child. The allergic condition is frequently called frequent colds, catarrh, or wet nose and

is thus dismissed as a matter of minor importance. The fact is that these popular names frequently serve to divert the attention of the physician from the fact that a perennial nasal allergy caused by milk or egg sensitiveness may exist.

The deformity referred to which is characteristic of nasal allergy in childhood is very different from that caused by adenoids or mouth breathing. It consists of a noticeable depression on each side of the nose most marked at first over the region occupied by the ethmoid cells. It starts beneath the inner canthus of the eye. In cases of longer standing, there is frequently a depression of the nasal process of the

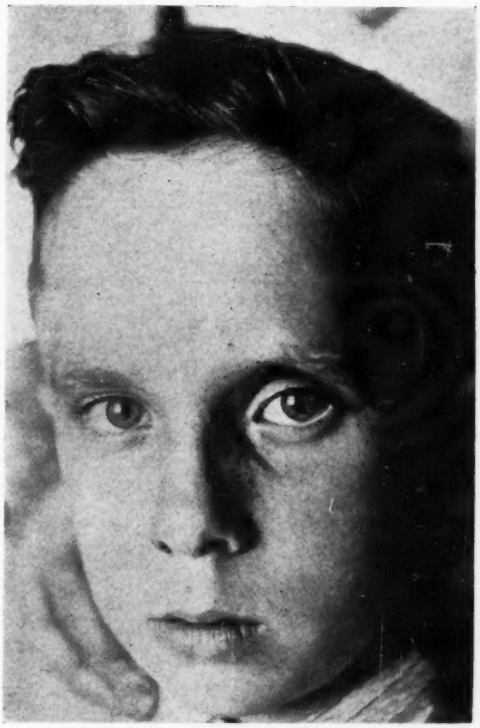

Fig. 2.

maxillary bone so that it loses some of its prominence. Also a depression below the anterior portion of the zygomatic arch in the areas over the antra may make its appearance. The paranasal depression or flattening often gives the nose undue prominence. Occasionally the nose appears stubby and "drawn in." Paranasal depression combined with depression below the zygomatic arch may give undue prominence to the cheek bones (zygomatic arch), causing a type of face which is very characteristic of the condition. This is very commonly observed in asthmatic adults.

This type of face is caused, I feel sure, by the fact that the ethmoid

cells and antra, because of defective aeration, do not develop adequately with growth of the patient's face.

It differs from the adenoid face in the absence of the pinched appearance of the nose, in the lack of prominence of the upper incisor teeth, and in the absence of the abnormal mouth and the abnormal lower jaw. It may resemble the adenoid face in the presence of an abnormally high arch in the mouth. The latter condition may be secondary to mouth breathing which is, of course, rather common in the case of nasal allergy.

The condition can make its appearance in young children within a year of the time of onset of a definite though not necessarily severe case of perennial nasal allergy. It can become less marked within a like time; that is, within one year or so if the nasal allergy is completely relieved. If the condition persists through the growing period into adult life, it becomes fixed and permanent. If perennial allergy in children is relieved soon after its time of onset, the deformity does not appear.

The deformity rarely appears in children with purely seasonal allergy even though the condition may be severe enough to cause complete stoppage of the nose. The fact is that if seasonal cases show this deformity, the physician should suspect the presence of perennial allergy in mild grade which he has overlooked.

The condition is frequently observed in patients whose dominant complaint is asthma. In fact, in many cases the complaint, asthma, may be so dominant as to distract the attention of both physician and parents from the fact that a nasal condition exists. The appearance of this deformity in an asthma case should indicate to the physician that nasal allergy does probably exist.

Adults with perennial asthma whose gross symptoms date from mature life rather frequently show this deformity and it indicates that they had nasal allergy in mild grade when they were young. In fact, a careful history in many such cases indicates that the patient did actually suffer from nasal stoppage, catarrh, or wet nose which was noticed during the growing period, but which attracted only casual attention.

This deformity of the face is so characteristic that if a series of perennial asthma cases should mingle with a series of normal individuals, it should not be difficult to pick out by the conformity of the face a gross majority of the asthma cases.

It seems that the appearance of a deformity in the face such as that described above should convince one of the urgency of taking seriously the condition, allergy, in growing children even though it be slight in grade.

DISCUSSION

DR. FRANCIS M. RACKEMANN, BOSTON.—I think Dr. Duke has made a real contribution in so far as he has given us all plenty to think about in connection with these young children. I am sure that, in so far as I am concerned at least,

the appearance of nasal allergy or bronchial allergy, is not thought of as often as it should be. In the future I shall certainly look for this sign. As to the secondary issue whether we should dignify this deformity by the term of "asthmatic face," I think that is open to discussion.

DR. PHILIP S. STOUT, PHILADELPHIA.—We find that in examining a number of children who have asthma and those who do not have asthma, but who have other symptoms, it is difficult to make a diagnosis by skin tests and by using various methods we have for finding chronic sinus conditions. A very large percentage of those chronic cases are suffering with sinus trouble, and I am very glad that Dr. Duke brought this out, because some of the teachers in the past who have specialized in the subject of sinus trouble have not believed it, nor have they taught it. Some years ago Beaudine and others suggested that children are probably almost as likely to have sinus trouble as adults.

DR. HORACE S. BALDWIN, NEW YORK CITY.—I would like to ask Dr. Duke whether he really favors the use of "allergic face" as the name of this condition. I have been struck with the idea that in many of these conditions of allergy the mucous membranes may react to allergens, but I rather question whether it is a definite and precise usage of the word to call such a condition an allergic condition to denote the pathology.

DR. M. A. RAMIREZ, NEW YORK.—A great many children and adults alike have the deformity described by Dr. Duke. Whether that deformity, however, is due to direct reactivity of the cell or to the result of mechanical obstruction and interference, is open to question. It again opens up the question of what allergy really is.

DR. ALEXANDER.—I am not quite clear as to the mechanism of this deformity. It presumably is a bony deformity. The recent work of Hansel shows that in allergy the bone is not involved unless an infection occurs. If that does occur, how can we distinguish between this infection and the other infections children get in sinus disease?

DR. W. W. DUKE.—I may not have made myself clear on this point. I am dead certain about the observation of the facts. I have seen it so many times, and I am sure all of you have, although you have made no particular note of it. There is no doubt that this is common in children with perennial nasal allergy. I think it is due not to a mechanical condition, but to the fact that the membranes are swollen and plugged with mucus so that air cannot get into the cells and allow the bones to develop. If the mouth is open the same thing occurs, for the teeth are pushed together by the weight of the cheek. The development of the bones of the face are due to vacuum and pressure under normal conditions.

When the child's nose and the openings in the nasal sinus are closed by swollen membranes, I do not think the cells can bloom out and develop as they ought to. It gives a permanent deformity to the face. I think this face is the result of a mechanical condition and not the cause of anything except its appearance and an abnormal breathing late in life. I do not believe that it is due to the peculiar reactivity of the cells of the bone at all; it is a mechanical condition. I think if the nose were plugged with mucus and the membranes were swollen perennially from some cause other than allergy, the same condition would be the result. The fact is that perennial allergy in children is the common cause of constantly swollen membranes, wet nose, etc. If you see the onset of this, find it developing, and then get rid of the cause, you will find it every year less marked. It thus makes you feel sure the cause of the deformity is mechanical. The same is true in the gross deformities of the chest which are seen in children with perennial asthma—some

have a pigeon breast, others have almost a hunched back. If that is due to a mechanical factor, traceable to the difficulty of getting the air in and out of the lung, then that the face should show a similar effect seems to me perfectly reasonable. I am uncertain about the use of the term "asthmatic face"; it is very typical of perennial allergy in childhood and is very noticeable.

Chemical and Clinical Studies on Pollen (Preliminary Report). ARTHUR STULL, M.D., ROBERT CHOBOT, M.D., AND ROBERT A. COOKE, M.D., NEW YORK CITY.

From a chemical and clinical study of pollen it was found that the material giving skin reactions in pollen-sensitive individuals was not destroyed by heating in the dry state as high as 150° C. Some activity remained after heating in neutral aqueous medium where hydrolysis had been reduced to a minimum. No votatile active product could be isolated by destructive or steam distillation of whole pollen. The P_H of pollen extracts in distilled water was distinctly acid after short extraction periods. The slightly alkaline bicarbonate extracting fluid favored the stability of the active material. Small amounts of norite, animal charcoal, kieselguhr, and alumina gel removed about one-half of the nitrogen from pollen extracts without showing marked diminution in skin tests.

Water extracts of pollen were precipitated by alcohol at from 90 per cent to 95 per cent concentration. The precipitate was found to contain most of the allergen. By reprecipitation an active water-soluble material was obtained containing nitrogen and only a trace of phosphorus. It reduced Benedict's solution and ammoniacal silver nitrate and after hydrolysis greater reduction was obtained. Arabinose has been isolated as an hydrolysis product. Solutions of such precipitates in dilutions giving skin reactions comparable to bicarbonate extracts contained about 90 per cent less nitrogen.

The skin-active material from defatted pollen was practically insoluble in ethyl ether, petroleum ether, chloroform, benzene, and absolute alcohol. A 70 per cent alcoholic extract of pollen gave evidence of at least two substances acting as allergens. One which is designated as substance "A" was soluble in aqueous extracts, 70 per cent alcohol, and hot 95 per cent alcohol. Its solutions gave reduction tests for pentoses and fermentable sugars. The second, called substance "B," was soluble in aqueous extracts but practically insoluble in 70 per cent alcohol; it was not extracted by hot 95 per cent alcohol but was inactivated by such treatment. The majority of cases reacted markedly to substance "A"; a few gave only slight reactions to "A" but marked reactions to "B." From the similarity in chemical behavior it seemed possible that substance "A" which in solution gave reducing substances and frothy solutions was a polysaccharide of a glucosidic nature possibly of a saponin type. Further chemical and clinical work is being conducted with the pollens along these lines.

DISCUSSION

DR. R. A. COOKE, NEW YORK.—I think it might be well to emphasize here that in the regular extracts as they are made today, watery extracts, etc., all of the essential components appear to be present and, therefore, from a practical standpoint there is perhaps nothing definite, or no obvious change that will take place in the immediate present in our handling of these cases for treatment. It also seems to me that it is quite obvious for the future of the work and the absolute investigation from the scientific and immunologic standpoint to know that we are dealing or have the capacity to deal with pure substances. It is, or has been, a very difficult thing to determine, and we feel we have finally found the presence of two different substances. To be sure, there may be more. It is also particularly interesting to find that in this work we have come across a substance, chemically related to the polysaccharide type of substance that is characteristic of the better known work in bacteriology. Of course, it means that if we can in the future handle pure substances, there may be eventually different processes of preparation of pollen extracts, and that our results should therefore be correspondingly improved. At the present time, however, we are only beginning the attempt to determine whether or not these substances in the form in which they are chemically isolated will have immunologic properties. Of course, it is known that with the polysaccharide substance from the pneumococcus no immunologic response is in itself obtained. It is only apparently an index of the type of response in the individual but the substance itself in its pure form, isolated apparently from its protein component, gives no immunologic response. It is, however, interesting to speculate on what may be the future outcome of studies of this kind. We hope that they will continue. The outlook at the present time is somewhat promising.

DR. A. H. W. CAULFEILD, TORONTO.—Dr. Stull was kind enough to refer to some work that my colleagues, Dr. Cone and Dr. Eddy, did with me about 1925. The biochemical work was done by Dr. Eddy, and we accomplished a little more than was published. Unfortunately for us, Dr. Eddy was given a good appointment to Cambridge and Dr. Cone a year afterward went to New York. We really never got an organization to go ahead with the objects we had in view. Although in that paper we called the precipitate, "An Albumin Proteose Mixture," Dr. Eddy was convinced that that was not the proper name.

I will not say any more about that, but I would like to say from what clinical experience I have had during about four years of utilizing first the ordinary control, and then the precipitate or dry powder, which I call albumin proteose, and the other that I call proteose, one thing has come out. There is a type of case which occurs, I should say, in 10 per cent that I will get a positive reaction, and I would miss it if I did not use those three testing materials. It is a small percentage, but on several occasions it has given me a good deal of pleasure to find those cases. I think I have obtained good results. As a matter of actual treatment, I make up three solutions. Where one of these is very pronounced in its reactions above everything else, I add it to the treatment.

Some Findings of Antral Studies With Iodized Oil in Patients With Bronchial Asthma. DR. PHILIP S. STOUT. (For original article, see page 446.)

DISCUSSION

DR. J. A. CLARKE, PHILADELPHIA.—We believe that we have a new method here for examining the sinuses and we think it gives us the most reliable data of any method that we have tried. The results by the other methods look very much like the recent Prohibition poll—a great many votes on each side. When the results of transillumination or of the flat x-ray plate are compared with the results from the

lipiodol, it will be seen that the lipiodol is much more accurate. There were only nine out of seventy-nine cases in which we did not feel we could make a definite diagnosis.

It is not a dangerous method. We have had no serious trouble. The most serious trouble was in the patient in whom lipiodol was injected under the eye. He complained bitterly for awhile, but that is all that happened. Where one might go wrong with the lipiodol injection, is in the failure to properly fill an antrum which has a thickened wall. The irregularity of the lipiodol shadow, due to the irregularity of the floor of the antrum, may be misleading. If these come to an acute angle, then the filling defects are probably due to either polyps or cysts. The thickened mucous membrane alone may cause trouble.

Only one patient was operated on who did not show disease of the sinus, and he was not operated on by Dr. Stout. This patient was operated on because the mucous membrane was thickened. Where there are great irregularities with filling defects, we believe there is a real pathologic condition in the antrum.

These patients who were sent to Dr. Stout were people who had been around the clinic many years. They had had x-rays and transillumination. The x-rays came back, one time positive and three months later normal. Then they went to a rhinologist and he washed the sinuses but found no pathologic condition because the washings came clear. In some of these at operation we have found the antrum literally loaded with polyps. We believe we have found a method of really diagnosing these obscure antrum cases.

DR. STULL, NEW YORK.—I should like to ask Dr. Stout what the ages of the children were when he did this, and how frequently he found pathologic conditions in children.

DR. MATTHEW WALZER, BROOKLYN.—What I have to say is possibly a little bit off the question. I have been scanning the literature waiting to hear reports of some untoward accidents following the use of lipiodol. We do hear of accidents following its use, and rather vague explanations as to what the cause may be. One aspect of the thing which I think is being overlooked is this: Lipiodol is made up usually (I do not know whether lipiodol is, but some of these oil preparations of iodine are) either of rapeseed oil or poppy seed oil. We have in atopic individuals distinct cases of rapeseed sensitivity and poppy seed sensitivity. They are not uncommon, because I have been testing for them routinely and I find definite reactions quite frequently. We have recently heard that in ragweed the oil of the plant is an active preparation and contains some of the active principle of ragweed. That is also true for cottonseed oil. I am just waiting and I think sooner or later we are going to hear of some lipiodol accident in an atopic individual. I think that as a general routine before there is any lipiodol injected into an atopic individual, regardless of where or how, some sort of preliminary test ought to be made with the oil to find out whether that patient can take the test. So far, as I say, we have not heard of any accidents, but I cannot see how we are going to avoid getting them sooner or later. I think we had better be on our guard.

DR. CAULFEILD, TORONTO.—We have done approximately over 1,500 lipiodol injections, nearly always for the detection of bronchiectasis. In about three cases out of that entire number reactions have occurred. I saw one reaction very early and I feel convinced it was anaphylactic. It never occurred to me that the patient might be sensitive. His tonsils were swollen, his eyes were red. He had no skin rash. We could not attribute it to iodine. It never occurred to me until now that it might have been allergic sensitivity. I am not speaking of the antra, but of the cases where bronchiectasis is suspected. This almost always is a different type of case. I am very glad to know of the possibility of this reaction.

DR. FERNAND VISTZREICH, NEW YORK.—Concerning the technic of this lipiodol injection of the sinuses, and especially of the maxillary sinus, I would like to mention a point which may perhaps be an improvement in the technic. I would like to find out if one has ever attempted to use the lipiodol in an atomizer, as a wave or spray, to fill out the cavities. To my mind, this would represent the antra in its extent, just as well as the complete filling of the sinuses, and at the same time it would reduce the amount to be injected about one-tenth, or one-twentieth, of its amount.

DR. ALEXANDER, ST. LOUIS.—I should like to call attention to an article about to be published in the JOURNAL OF ALLERGY by Dr. Proetz, who was instrumental, I believe, in introducing this method of lipiodol injection of sinuses. This describes a hypersensitive individual who was sensitive to feathers. Her lipiodol pictures were extremely interesting, and showed a very small amount of lipiodol in one or both antra—I have forgotten which. She was then taken off feathers, and in a short time thereafter the antra looked entirely normal, showing that the swelling of the mucous membrane of the nose also extended to the mucous membrane of the sinuses. The mere appearance of only a small amount of lipiodol, I think, perhaps should be investigated along those lines.

DR. PHILIP STOUT.—Answering Dr. Alexander's question first, frequently we do give a second injection. We want to be sure we are right before we do anything radical. Of course, it is hard to conceive of that thin mucous membrane swelling up half an inch, but it does happen. One can be easily fooled if he is too radical in his operative procedure.

I have never used the spray. I do not think the oil can be sprayed. The fact that it goes into every crevice and shows the polyps makes it particularly helpful.

As to the danger, of course, there is danger. There is danger in vaccination. It is possible that we may try to prevent any accident by testing these patients for poppy seed, or whatever is used in these oils. There is more than one kind of oil. One would probably have to try them all out if he used different substances, to find out what each contains.

As to age, I think the youngest patient was four years old. It is hard to believe that a four-year-old youngster will let you inject both antra with lipiodol. It is possible. You simply have to explain it, and it is wonderful how reasonable these patients are. I have had several five-year-old patients. So far we have found only a slight pathologic condition in these youngsters, but no doubt it is there.

Observations on Certain Castor Bean Extracts. JAMES H. BARNARD, M.D., NEW YORK CITY.

This paper is a report of 7 patients who were sensitive to extracts of castor bean and a study of the extracts of castor bean. The ricin present in some of these extracts has been removed without altering their activity, although by its removal they were made nontoxic; extracts of unusual activity have been made and dilutions that are safe for testing patients sensitive to the castor bean have been demonstrated.

The active principle or principles have been shown to be soluble in water but precipitated by alcohol; they are not precipitated or destroyed by boiling and are not dialyzable.

DISCUSSION

DR. WARREN T. VAUGHAN, RICHMOND.—I should like to ask Dr. Barnard whether he has tested these patients with castor oil, and whether there is any possibility of symptoms from the taking of castor oil for medical purposes. We should always bear in mind the possibility of castor bean sensitization. There have been only a few reports. Figley reported several cases in a castor bean factory in Toledo. He mentions quite an epidemic, if you might call it that, in Connecticut. Dr. Figley gave me some of his castor bean dust and I had three or four obscure cases in a fertilizing factory in Suffolk, Virginia, who had come up to Richmond to be tested. I found them sensitive to this castor bean meal which I obtained from Figley, and told them to go home and see whether there was any castor bean meal in the fertilizer. They not only found that there was castor bean meal in the fertilizer, but that it had been obtained in Toledo, from the same factory where there had been trouble. Where fertilizer is distributed, one must bear in mind the distinct possibility.

DR. R. A. COOKE, NEW YORK.—I think it might be well to emphasize one thing; that is, the very extraordinary degree of sensitivity with these extracts. I do not think we have found so far any other single preparation that requires use in the dilutions that are necessary here in order to avoid the very uncomfortable constitutional reactions that were reported by the early workers. It does not suffice to make dilutions on the basis of our nitrogen determinations comparable even with the pollens. Our routine test, as a matter of fact, begins with the dilution of 0.001 milligrams of nitrogen and indications of positive reactions are many times obtained even in such dilutions. With the constitutional reactions it is quite obvious from this why serious results were obtained when these very strong extracts were used for intradermal tests in the cases that have already been reported.

A Report of the Incidence of Allergy in a Group of Cases Developing Postoperative Atelectasis. DR. H. B. WILMER. (To be published in a later issue.)

A Study to Enumerate the Foods Occurring in, and Their Influence Upon, the Various Clinical Types of Allergic Nasal Reaction. C. H. EYERMANN, ST. LOUIS. (For original article, see May issue.)

DISCUSSION

DR. BALDWIN, ROCHESTER.—I am very much interested in Dr. Eyermann's paper, particularly in the cases of perennial vasomotor rhinitis. I have seen a number of patients recently that gave positive skin reactions who were definitely improved by diet restriction. I should like to ask him whether he tested the mucous membranes of these patients with seasonal hay fever by the installation of pollen directly into the nose to find out whether they were sensitive or not. It seems rather unusual that restriction alone would influence the symptoms of the seasonal hay fever. In other words, possibly they were not hypersensitive to pollen—at least, the mucous membranes were not.

DR. RACKEMANN, BOSTON.—I should like to know how frequently Dr. Eyermann found that it was necessary to eliminate wheat and other cereals in considerable amount. I mention that because I feel quite sure that the total dietary must be quite important in a good many of these patients. Some of the patients illustrate the fact that in certain seasons the treatment with pollen in one season may be followed by freedom from symptoms in the next season despite the absence of treatment.

DR. C. H. EYERMANN.—The mucous membranes were not tested directly by the application of pollen. In these individuals the skin may have been sensitive to pollen and the nasal membranes not. The fact remains that the patients with hay fever came in for the purpose of being treated for hay fever. Pollens were responsible in thirty instances in the series, with the common foods, wheat, milk, and eggs being next in frequency. What was striking to me was the frequency with which fruits enter into the problem as a group. As a group they accounted for about twenty-four instances. Thirteen varieties of fruit were in the group. Another important factor perhaps seems to be chocolate.

The Significance of Local Reaction in the Skin Following Deep and Superficial Injection of Pollen Extracts. LESLIE N. GAY, BALTIMORE, MD. (For original article, see page 403.)

DISCUSSION

DR. PHILIP LEVINE, NEW YORK.—Certainly Dr. Gay demonstrates a striking difference between the injection of the extract intradermally and the injection of the extract into the subcutaneous tissue. Immediately one wonders whether this difference is reflected in the therapeutic end-results. Of course, this is a question that must be decided. On the other hand, it may be assumed that the wheals are not only confined to the skin but are also present in the subcutaneous tissue. That is difficult to test. One way of testing it perhaps would be to use a method recently used by Froin, that of grinding up the tissue and attempting to demonstrate the antibodies.

DR. LESLIE N. GAY.—With regard to Dr. Levine's question as to the therapy, I believe that, considering the figures with which I am familiar and those of men working in the same field, our figures compare favorably with theirs. I will not go into the figures with regard to our results now, but at a future time they will be published.

I do not deny that the reagins are present in all tissue. The question I have raised is whether or not we are entirely overlooking the anatomic structure of the skin in our method of treatment.

Linseed Meal Sensitization. GRAFTON TYLER BROWN, M.D., WASHINGTON, D. C.

The vast literature on allergy contains occasional references to sensitization to flax, flaxseed, or linseed, and these references are reviewed somewhat completely. A general description of flax and its products is given to show the numerous ways in which a person hypersensitive to the flax proteins may come in contact with them. Several typical cases of linseed meal sensitization are reported by the writer.

Although sensitization to flaxseed or linseed is one of the less commonly encountered forms of hypersensitiveness, it is of sufficient importance to merit careful consideration in diagnosing and treating asthma, nonseasonal hay fever, dermatitis, or urticaria, especially in persons, such as farmers or nurses, who come in contact with these substances. Sensitization to the protein of flaxseed or linseed is usually very marked, and the best method of detecting it is by means of the cutaneous or "scratch" test, using ordinary linseed meal and moistening it with a drop or two of tenth-normal sodium hydroxide solution. Specific desensitizing injections of a linseed meal extract may be given with perfect safety, provided sufficient care and judgment are used in determining the initial and subsequent doses.

Department of Reviews and Abstracts

Selected Abstracts

Bertcye, P., and Dechaume, J.: Encephalitic Lesions in a Case of Serum Anaphylaxis in a Child of Eight Years. Lyon Méd. **144:** 762, 1929.

A case report is given in detail of a child, aged eight years, suffering from a disseminated purpural eruption following an attack of scarlet fever. The purpura was of great severity and did not yield to ordinary therapeutic measures. A subcutaneous injection of 10 c.c. of horse serum was given, but no relief was obtained.

Thirty-six days later antidiphtheria serum was given to promote mild anaphylactic shock which might exert some beneficial effect upon the state of the blood. Eight c.c. of antidiphtheria serum mixed in salt solution was administered intravenously within four minutes. Five minutes later the child died in shock. At autopsy, interesting lesions were observed in the nerve centers. Examination of a stained section of the cord sheath showed no modifications of the meninges. Attention is drawn to two sorts of lesions: (1) Around certain vessels in the parenchyma, a hemorrhage of the nerve sheath was observed. The perivascular spaces were filled with red blood cells. (2) Some capillaries showed in their lumina masses of white blood cells, particularly polynuclears, which filled the entire vascular cavity. This was not accompanied by cellular passage in the perivascular spaces. The impression was of a leucocytic thrombus blocking the lumen.

The authors conclude that such accidents, notably the hemorrhagic condition in the cord, might be attributable to purpura were this the only case of its kind examined; but comparison with lesions in other cases of deaths from anaphylaxis incline them to believe it due to shock.

Morey, J. B., and Michie, T. C.: Physical Allergy Due to Heat and Exhaustion. Proceedings of the Staff Meetings of the Mayo Clinic **5:** 74, 1930.

A case is reported in detail of a patient whose attacks of generalized urticaria, for a period of five years, had been brought on by exposure to heat or by exercise or by a combination of the two. The attacks lasted from fifteen to twenty minutes, were of increasing frequency, and were followed by a feeling of exhaustion. Laboratory examination, including skin tests, gave negative results.

During the patient's stay in the hospital attacks were precipitated by various methods, such as hot baths, hot drinks, wrapping in blankets, exercise under a carbon arc lamp, etc. It was discovered that some immunity could be developed by a regimen of exposure to the exciting conditions. Such immunity, however, was not lasting. Attacks, both spontaneous and induced, again occurred.

The patient was then placed under a histamine treatment, administered subcutaneously. The patient was finally dismissed with directions to take histamine for two weeks with gradually increasing doses followed by two weeks of rest.

The patient, reporting every two to four weeks for the four and one-half months since dismissal, states that her condition is improved 80 per cent both for the two weeks while she is taking histamine and for the two weeks of rest. If the rest period is longer, the urticaria is more frequent and the feeling of exhaustion again occurs. Relief is obtained as soon as the histamine injections are again taken.

Szegö, L.: True Bronchial Asthma in a Nursling. Ztschr. f. Kinderh. **48**: 581, 1929.

It has been held that in children bronchial asthma and asthmatic bronchitis are two distinct disease pictures. The differences between them depend upon the following: (1) The first true asthmatic attack occurs usually after the first year and a half of life and seldom before the close of the first year; the first attack of asthmatic bronchitis, on the contrary, occurs very frequently at this age. (2) Repeated attacks of asthmatic bronchitis can occur, but in contradistinction to true asthma the tendency is to decrease after a short period. (3) Asthmatic bronchitis never goes over into true asthma. (4) Asthmatic bronchitis always begins with a cold; bronchial asthma sets in without any previous infection of the upper respiratory passage. (5) In asthmatic bronchitis there is never an eosinophilia. (6) In asthmatic bronchitis there is not the association with eczema found in asthma. (7) In asthma there is, for the most part, an hereditary factor not present in asthmatic bronchitis.

The author states that the newest literature on the subject is not in sympathy with this sharp differentiation between the two pictures. He gives in detail a case of his own in support of this newer viewpoint. The patient was a six-months-old child of healthy parents with no hereditary history of asthma. The child had suffered a "lung catarrh" for three months, with cough and a fever for one week. One day it caught a slight cold and coughed a little. It then vomited after taking the bottle and one hour later difficult asthmatic breathing set in which rapidly became worse. The child became cyanotic and cold, and in spite of all therapeutic measures died about sixteen hours later. On autopsy both lobes of the lung were distended. From the small bronchi a pur-

ulent fluid could be pressed out. There was a swelling of the lymph nodes. Microscopic section showed in the lung the picture of emphysema. In many of the bronchi the infiltration consisted almost entirely of eosinophile cells.

The findings, in short, conform with those of bronchial asthma. In support of the view that this is a true case of bronchial asthma, the author discusses it in detail in connection with the seven points previously mentioned as the marks of differentiation between bronchial asthma and asthmatic bronchitis in children. He concludes that the conditions described above under two different names are those of bronchial asthma which occur much oftener in nurslings than heretofore has been supposed.

Harkavy, J., and Hebold, S.: Bronchial Asthma and Pulmonary Tuberculosis. Am. Rev. Tubere. **21**: 644, 1930.

The relationship between bronchial asthma and pulmonary tuberculosis is considered from the following angles: (1) What rôle does true hypersensitiveness to foreign proteins play in the causation of asthmatic symptoms in tuberculosis patients? (2) What part does nonspecific infection play in the induction of asthmatic attacks?

From four hundred cases of bronchial asthma which showed clinical and x-ray evidence of pulmonary tuberculosis, eighteen cases were selected. Of these eighteen, nine were insensitive to skin tests and nine gave evidence of protein hypersensitivenss to inhalants. Of the sensitive patients, only six were available. Although they gave multiple skin reactions, reagins to only one or two proteins were found on passive transfer.

Following the removal of the offending protein, the clinical course of the sensitive patients proved satisfactory as far as their asthmatic symptoms were concerned.

The progress of the nine nonsensitive asthmatics was less favorable. Of these, six had chronic sinusitis, two bronchiectasis, and one, a chronic focus of organized pneumonia.

The authors conclude that in the protein-sensitive group, the foreign proteins of the inhalant group and not the tubercle bacillus were responsible for the asthma. In the nonprotein sensitive group the asthma was ascribed to the complicating respiratory infection and not to the tubercle bacillus.

Müller-Deham, A., and Lasch, F.: Old-Age Asthma and Allergy. A Diagnostic and Therapeutic Study. Deutsch Arch. f. klin. Med. **165**: 354, 1929.

It had been noted by one of the authors that in old age a form of dyspnea, which in its clinical manifestations was closely allied to bronchial asthma, played a very important rôle. Bronchial asthma is gen-

erally considered in the literature on the subject as a specific allergic disease. The question then arose whether the so-called old-age asthma is an allergic disease and whether it might yield in measure to specific therapy.

Skin tests with the antigens and technic employed by Storm van Leeuwen were given to twelve patients suffering from asthma-like dyspnea. One-tenth c.c. of the solution was injected intracutaneously and a control of phenol-saline solution was used. The twelve patients were divided into two groups: (a) five patients of the purest type of bronchial asthma with the sharpest attacks and in whom the bronchitis was reduced to the minimum; (b) seven patients whose dyspnea was of the bronchial asthma type but whose attacks were not so sharp. Positive skin reactions were obtained to only three allergens. Two bacterial allergens were made from the sputum of patients with asthma and bronchitis and from moulds. All twelve patients gave plus reactions. Both groups of patients reacted with the same intensity to these allergens.

The specificity of this reaction, however, was questionable due to the fact that control cases of elderly individuals free from asthma also gave a high percentage of positive reactions to moulds and bacterial extracts.

The twelve patients were treated by series of injections of antigen made from the allergens to which they reacted in an attempt at desensitization. In only two cases were no beneficial results obtained. In the remaining cases there was marked improvement. The authors state, however, that the treatment could not with certainty be considered specific.

Cohen, M. B., and Rudolph, J. A.: Hay Fever. The Importance of Substances Other than Pollen in the Etiology; Their Influence on Seasonal Cure. Arch. Int. Med. **45**: 742, 1930.

In spite of preseasonal treatment for hay fever, there are patients who obtain no relief from their symptoms and others who obtain only partial relief. It is suggested that many of these might obtain full relief if attention were paid to various factors that have been pointed out before but not generally stressed. A review of the histories of one hundred patients with ragweed hay fever showed that 30 per cent had symptoms at other times of the year. These symptoms were so slight that often they were overlooked. All of these patients gave reactions to some substance other than ragweed pollen.

Case reports are given to show that a discovery of the complicating sensitivities and the elimination of contact with them or desensitization to them, may result in a complete seasonal cure. Some of the more common of these complicating factors are given as: (1) Other pollens. (2) Dusts. Here the reacting substance is thought to be probably a

mould or some other type of organism which contaminates the furniture from which the dusts are made. The allergen is not to be confused with the house dust atopen of Coca. (3) Orris root. (4) Epidermal proteins. (5) Foods.

Burckhardt, J. L.: The Relationship of Asthma and Weather Conditions. Schweiz. med. Wchnschr. **60**: 149, 1930.

A study of the effect of climatic conditions upon asthmatic patients, both children and adults, was made at the Davoser Physical-Meteorologic Institute in Switzerland. A considerable number of asthmatic patients were observed over a period of several years. The periods (days and months) in which the patients suffered most were observed and recorded and the meteorologic conditions given. It was concluded that atmospheric pressure had no appreciable effect, nor did any contamination, organic or inorganic, of the air. The only factors that seemed to have any definite connection with the frequency or severity of attacks were atmospheric depressions, such as fog, rain or snow, and in the mountains, sudden cold changes. Mere altitude had no effect.

Chobot, R.: The Coincidence of Sinusitis in Asthmatic Children. Am. J. Dis. Child. **39**: 257, 1930.

One hundred cases of asthma in children up to fifteen years of age were selected. All patients were tested intracutaneously with extracts made according to Coca's method. Only 15 per cent gave negative reactions. Forty-one per cent showed sinus involvement. The criteria were positive roentgenograms checked by clinical observations.

Case reports of three patients are given in detail, showing the efficacy of combined treatment. The patients were either removed in so far as possible from contact with the offending protein, or desensitization was attempted. Concomitant with this treatment, nose and throat therapy was instituted.

It is suggested that for the best results in these asthmatic cases there should be close cooperation with nose and throat specialists.

Penfound, W. T., and Efron, B. G.: A Standardized Method for Pollen Air Analysis. Society for Experimental Biology and Medicine **27**: 650, 1929.

An apparatus is described which is designed to determine more accurately the relative percentage of pollens falling or being supported by the air at a given time. The apparatus consists of a sensitive weather vane made of sheet metal, on which are mounted two slots (one horizontal and one vertical) into which microscopic slides which catch the pollen are inserted. It was found that the vertical slides showed a relatively greater number of pollens on windy days, and the horizontal

slide a greater number on calm days. The ratio of the number of pollens on the vertical slide to that on the horizontal is called the buoyancy index. The buoyancy indices of ragweed, elm, and cedar showed: ragweed, four; elm, five; and red cedar, two.

Ratner, B.: A Possible Explanation for Horse Serum Anaphylaxis in Man. J. A. M. A. **94**: 2046, 1930.

Three cases from the author's personal experience and further cases from the literature on the subject are cited which showed severe anaphylactic symptoms, sometimes terminating in death, after an initial injection of horse serum. Artificial sensitization to horse serum, except in one possible instance, was ruled out. It has been suggested that persons with asthma caused by contact with horses may be naturally sensitive to horse serum. In this view the author concurs and offers his own experimental evidence. He found that in guinea pigs sensitized to horse dander extract, death often resulted from initial intravenous injection of horse serum. In other words, a crossed relationship between horse dander and horse serum exists. Moreover, guinea pigs could be sensitized to horse dander by inhalation, a portal of entry favorable to spontaneous sensitization in man. It is suggested by the author that the natural sensitization to horse serum through the inhalation of horse dander demonstrated in the guinea pig must explain the phenomenon in man. Such individuals as are shown to be sensitive to both horse dander and horse serum should be regarded as risks for the primary injection of horse serum. In such cases serum should be administered only when absolutely necessary and with the utmost precaution. The author believes the artificially sensitized person is somewhat less susceptible to severe serum accidents than the patient with genuine horse asthma.

Coates, G. M., and Ersner, M. S.: Occurrence of Eosinophils in the Mucous Membrane of the Maxillary Sinus in Asthmatic Patients. Arch. Otolaryng. **11**: 158, 1930.

In analyzing a group of cases it was found that in about 75 per cent nasal polypi were secondary to other pathologic processes in the maxillary sinuses and a considerable percentage culminated in asthma. In the group of asthmatic patients associated with suppuration of the maxillary sinus eosinophiles were found in large proportion. Normally, in an ordinary blood count from the mucous membrane, one eosinophile is found to the average count. In acute infections there is an increase in the polymorphonuclear leucocytes and in chronic infection an increase in lymphocytes. It might be expected that with the increase of polymorphonuclears and lymphocytes the eosinophile count would disappear. It was found, however, that in the asthmatic patients under ob-

servation the eosinophile was present in the mucous membrane in addition to the purulent conditions in that membrane.

Therefore, the authors conclude that there is a logical assumption that asthma and the presence of eosinophiles in the mucous membrane are closely associated.

Seegal, D., and Seegal, B. C.: Local Organ Hypersensitiveness. I. Experimental Production in the Rabbit Eye. Proc. Soc. Exper. Biol. & Med. **27**: 390, 1930.

The question of the possibility of local allergic reactions in the eye was definitely established in the affirmative by a specialized technic. This depends on keeping a specific foreign protein in contact with local tissues for a comparatively long time. Foreign red blood cells and egg white were injected into the anterior chambers of rabbits. Six days thereafter the absorption was apparently complete and the injected eye was apparently restored to normal. After the usual antianaphylactic interval, an intravenous injection of the specific protein was given. No shock or other evident symptoms occurred. Within five hours, however, the sensitized eye became markedly swollen and injected. This is apparently a strictly local allergic phenomenon and lasts usually twenty-four hours.

Seegal, D., and Seegal, B. C.: Local Organ Hypersensitiveness. II. Repeated Response in the Rabbit Eye. Proc. Soc. Exper. Biol. & Med. **27**: 393, 1930.

Multiple antigens were used to sensitize the eye, and it was found that after the antianaphylactic period, the eye would respond by inflammation to intravenous fractions of the total antigen. In this way, the eye could be kept in a more or less constant state of inflammation. Although reactions to a single antigen elicited six or seven months after sensitization are less intense than the initial responses, permanent desensitization did not occur. On one occasion inflammation of a sensitized eye occurred after the introduction of the antigen through a stomach tube.